Briefing Document

Endocrinologic and Metabolic Drug Advisory Committee

April 01, 2014

NDA 022472

AFREZZA®
(insulin human [rDNA origin]) Inhalation Powder

An ultra-rapid acting insulin treatment to
improve glycemic control in adult
patients with diabetes mellitus

Advisory Committee Briefing Materials: Available for Public Release

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LIST OF ABBREVIATIONS

Abbreviation	Definition or Explanation
ADA	American Diabetes Association
ADME	absorption, distribution, metabolism, and excretion
AE	adverse event
AFREZZA®	drug/device combination product consisting of Technosphere Insulin Inhalation Powder (TI), the inhaler, and the cartridges containing TI; sometimes referred to as Afrezza Inhalation System or TI Inhalation System
ANCOVA	analysis of covariance
AR	autoregression
ATS	American Thoracic Society
AUC	area under the concentration-time curve
BA	bioavailability
BAL	bronchoalveolar lavage
BE	bioequivalence
BG	blood glucose
BID	twice daily
BMI	body mass index
BPR 70/30	premixed biphasic rapid-acting analog of insulin (70% intermediate-acting insulin + 30 rapid-acting insulin)
CFR	case report form
CI	confidence interval
C_{max}	maximum observed concentration
COPD	chronic obstructive pulmonary disease
CRL	Compete Response Letter
CSR	clinical study report
CV	coefficient of variation
%CV	percent coefficient of variation
CVD	cardiovascular disease
DAWN	Diabetes Attitudes, Wishes, and Needs
DCCT	Diabetes Control and Complication Clinical Trial
DDI	drug-drug interaction
DKA	diabetic ketoacidosis
DM	diabetes mellitus
DNA	deoxyribonucleic acid

Abbreviation	Definition or Explanation
DPP-4	dipeptidyl peptidase 4
EASD	European Association for the Study of Diabetes
ECG	electrocardiogram
E_{max}	maximum effect
EGP	endogenous glucose production
EOT	end of treatment
EQ-5D	EuroQol 5D Assessment of Health Outcomes instrument
ERS	European Respiratory Society
FAS	full analysis set
FDA	Food and Drug Administration (of the United States)
FDKP	fumaryl diketopiperazine
FEV_1	forced expiratory volume in 1 second
FMEA	Failure Mode and Effects Analysis
FPG	fasting plasma glucose
FVC	forced vital capacity
GEE	generalized estimating equation
GIR	glucose infusion rate
GIR AUC	glucose infusion rate area under the curve
GIR t_{max}	time to maximum glucose infusion rate
GIR_{max}	maximum glucose infusion rate
GLP-1	glucagon-like peptide-1
HbA1c	glycosylated hemoglobin
HCP	healthcare provider
IAB	anti-insulin antibody
IND	Investigational New Drug
ITQ	Insulin Treatment Questionnaire
ITT	intent-to-treat
IU	international units
IV	intravenous
LLN	lower limit of normal
LOCF	last observation carried forward
LS	least squares
MDI	multiple-dose insulin
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent-to-treat

Abbreviation	Definition or Explanation
MKC	MannKind Corporation
MMRM	Mixed Model Repeated Measures
NA	not available or not applicable
NDA	New Drug Application
NHANES III	Third National Health and Nutritional Examination Survey
NPH	neutral protamine Hagedorn
OAD	oral antidiabetic drug(s)
PD	Pharmacodynamics(s)
PFL	pulmonary function laboratory
PFT	pulmonary function test
PK	pharmacokinetic(s)
PP	per protocol
PPG	postprandial glucose
PRO	patient-reported outcomes
QT	time from the beginning of the QRS complex to the end of the T-wave (on an ECG)
QTc	corrected QT
QTcI	individually-corrected QT
RAA	rapid-acting analog (of insulin)
RIA	radioimmunoassay
rDNA	recombinant deoxyribonucleic acid
RHI	regular human insulin
SAE	serious adverse event
SC	subcutaneous
SD	standard deviation
SE	standard error
SEM	standard error of the mean
SMBG	self-monitoring of blood glucose or self-monitored blood glucose
SU	sulfonylurea
$t_{1/2}$	half-life
TEAE	treatment-emergent adverse event
TI or TI Inhalation Powder	Technosphere® Insulin Inhalation Powder
TI Gen2	Technosphere® Insulin (Inhalation Powder) administered with the Gen2 Inhaler

Abbreviation	Definition or Explanation
TI Inhalation System	see Afrezza
TI MedTone	Technosphere® Insulin (Inhalation Powder) administered with the MedTone inhaler
T1DM	type 1 diabetes mellitus
T2DM	type 2 diabetes mellitus
t_{max}	time to reach C_{max}
TP	Technosphere® Powder (Technosphere® Inhalation Powder without insulin) or Technosphere® particles; serves as a placebo control for TI
U	unit
URI	upper respiratory tract infection
US	United States
V	visit
W	week

1 EXECUTIVE SUMMARY

MannKind Corporation (MKC) is seeking approval for TECHNOSPHERE® Insulin Inhalation System (AFREZZA®) for the following indication: to improve glycemic control in adults with type 1 or type 2 diabetes mellitus (T1DM or T2DM) (NDA 022472). This drug/device combination product delivers insulin via a non-injectable, oral inhalation route. Technosphere Insulin Inhalation Powder (TI) is composed of recombinant human insulin and fumaryl diketopiperazine (FDKP), an inert excipient. It is administered with the breath-powered, dry powder Gen2 inhaler that provides ease of use and consistent, reproducible insulin delivery.

Inhaled TI is an ultra-rapid acting insulin with a more rapid onset/shorter duration of action than either subcutaneous (sc) regular human insulin (RHI) or sc rapid-acting analog (RAA) insulins. This unique pharmacokinetic (PK) profile more closely mimics mealtime endogenous insulin secretion. TI is administered either immediately before or within 20 minutes after starting a meal, as part of an individualized diabetes treatment regimen. It must be used with basal insulin in patients with T1DM and may be used with either oral antidiabetic drugs (OADs) or basal insulin in patients with T2DM. The TI Inhalation System has been extensively evaluated in clinical trials in these populations.

Background
Diabetes mellitus (DM) is a chronic disease increasing in prevalence worldwide. Effective DM treatment is critical in managing the disabling and life-threatening long-term complications of diabetic microvascular and macrovascular disease. Patients with T1DM should be treated with a multiple-dose insulin (MDI) regimen or insulin pump therapy; use of insulin that is associated with less hypoglycemia (ie, insulin analogs) is recommended. For patients with T2DM not at glycemic goal with diet and exercise, treatment guidelines recommend starting OAD monotherapy, typically metformin, and, if target hemoglobin A1c (HbA1c) goals are not achieved within 3 months, adding a second oral agent, a GLP-1 receptor agonist, or insulin. Ultimately, due to progressive β-cell dysfunction in T2DM, many patients, particularly those with long-standing disease, will require and benefit from insulin therapy.

Despite the importance of glycemic control and the availability of a range of therapeutic options, a substantial number of DM patients do not achieve recommended glycemic targets. An impediment to effective DM control has been termed “clinical inertia” (the lack of initiation or intensification of therapy when clinically indicated). Although the most effective glycemic control will be obtained with insulin therapy, data suggest that there is considerable delay in insulin initiation by health care providers (HCPs). Several population-based studies suggest that the average patient with T2DM experiences a 5-year delay from combination OAD therapy failure in glycemic control to the start of insulin therapy. Such delays subject patients to the risks of a considerable cumulative glycemic burden.

Patient barriers to effective use of insulin therapy also exist, and include factors such as psychological and diabetes-specific distress, lifestyle and convenience issues, complicated insulin regimen, fear of needles/injections, and fear of weight gain. One-third of HCPs report that their insulin-using patients are concerned about their injections; a similar number of

people with DM who use insulin injections report dreading them. Lack of compliance with an insulin regimen is a problem in both T1DM and T2DM patients, as noted by frequent dose restriction or frank omission of insulin injections. Ultimately, however, hypoglycemia (and the fear of it) is the limiting factor in achieving glycemic control in patients with DM. Episodes of hypoglycemia not only cause recurrent physical and psychological morbidity and risk of death in the short term, but also hinder long-term achievement/maintenance of near-normal glucose levels.

Barriers that limit effective glycemic control and impede compliance with starting/maintaining insulin therapy, such as clinical inertia, suboptimal insulin dosing and use, and fear of weight gain and hypoglycemia, contribute substantially to a patient's glycemic burden. Earlier initiation of insulin remains an important unmet medical need. New insulin therapies that provide convenience, ease of use, and clinical benefit could be important additional therapeutic options for individualized DM management.

Regulatory History and Clinical Development

The TI clinical development program has been guided by a number of regulatory interactions. Original NDA 022472, submitted to the FDA in March 2009, presented clinical efficacy and safety data of TI delivered using the MedTone inhaler. The FDA response (Complete Response Letter [CRL] March 2010) requested additional data to establish the clinical utility of TI in the treatment of DM.

The NDA was amended in June 2010 to propose the Gen2 inhaler (a new inhaler and cartridges) as the to-be-marketed device utilizing the same TI formulation. The Gen2 inhaler and cartridge were designed to provide insulin exposure equivalent to the MedTone inhaler, while providing greater ease of use. In vitro performance and comparative PK bioequivalence data were submitted to bridge the Gen2 inhaler to the earlier Phase 3 trials conducted with the MedTone inhaler.

In a second CRL (January 2011), the FDA requested that MKC conduct 2 randomized, controlled, Phase 3 clinical trials using the Gen2 inhaler: 1 trial in subjects with T1DM and 1 trial in subjects with T2DM. One of the trials had to include the MedTone inhaler in addition to the Gen2 inhaler to allow for a head-to-head comparison of pulmonary safety data for the 2 devices. The FDA also requested Gen2 inhaler dose-proportionality data and a human factors evaluation.

The current 2013 NDA Resubmission includes new clinical trial data to address the issues noted in the CRLs. In addition, this submission provides pooled safety data from the 2 prior submissions plus new data for a comprehensive overall safety assessment in more than 3000 T1DM and T2DM subjects treated with TI.

Drug Product

Afrezza is a drug/device combination product consisting of TI pre-filled into single-use cartridges and the Gen 2 inhaler. Technosphere particles are prepared by the pH-controlled crystallization of FDKP, a biologically inert excipient. The Technosphere particles consist of FDKP, polysorbate 80, and trace amounts of acetic acid and water. Human insulin produced

by recombinant deoxyribonucleic acid (rDNA) technology is adsorbed onto carrier Technosphere particles whose formation is reproducible and well controlled.

Upon administration, TI Inhalation Powder particles are inhaled into the lungs, where they dissolve immediately. The low bulk density, uniform particle size, and tight particle size distribution centered around 2 microns provide excellent aerodynamic properties that facilitate uniform distribution to the deep lung following inhalation. FDKP does not facilitate drug absorption, but functions solely as the particle matrix to carry the insulin to the lung. Once the particles dissolve, both the FDKP and the insulin are absorbed passively and independently of each other. This rapid dissolution provides an insulin PK profile that results in an ultra-rapid onset of insulin action. The absorbed FDKP is not metabolized and is excreted intact, primarily in the urine. The small amount of FDKP deposited in the throat during inhalation and subsequently swallowed is excreted intact in the feces.

Users self-administer TI by oral inhalation using the Gen2 inhaler. The to-be-marketed cartridges contain either 0.35 mg (10 U) or 0.7 mg (20 U) of insulin. The 10 U cartridge approximates 3 units of sc injected insulin (and is labeled as “3 units”) and the 20 U cartridge approximates 6 units of sc injected insulin (and is labeled as “6 units”).

The Gen2 inhaler is small, discrete, easy to use, and is discarded and replaced every 15 days. The user’s inhalation effort reproducibly delivers TI to the lungs. Extensive testing, including monitoring of subject use in various clinical trials, shows that delivery of the powder occurs with inhalation efforts easily achieved by subjects. A comprehensive, summative human factors usability validation trial has been conducted on the final to-be-marketed TI Inhalation System with the Gen2 inhaler. Results demonstrate that the TI Inhalation System can be correctly, safely, and effectively used by the intended user population, including patients with neuropathy, retinopathy, and color-blindness. More than 5,000 Gen2 inhalers have been dispensed to subjects in clinical trials. Few device complaints were received; where appropriate, they were addressed by subject education efforts in the Instruction-for-Use (IFU).

Compared to its predecessor MedTone device, the Gen2 inhaler is smaller, has fewer parts, requires fewer steps for use, and needs only one inhalation per cartridge. The Gen2 inhaler is more efficient than the MedTone inhaler, with 33% less TI needed to provide the same insulin exposure. Equivalence of TI Inhalation Powder delivered by both inhalers (MedTone and Gen2) has been shown. A head-to-head comparison of the inhalers has demonstrated comparable pulmonary function test (PFT) results over 24 weeks and similar overall pulmonary safety profiles.

Nonclinical Development

Insulin has been in clinical use for DM treatment for decades. The AFREZZA nonclinical program provides full characterization of the systemic effects of Technosphere particles without insulin (TP) and of the potential adverse effects of both TI and TP on the respiratory system, when administered primarily via the pulmonary route. No unexpected safety signals have emerged with TI and TP in an extensive nonclinical program including Safety, Pharmacology, PK/ADME, Single-dose and Repeat-does toxicology, Genotoxicity, Carcinogenicity, and Reproductive and Developmental Toxicology. TI and TP are well

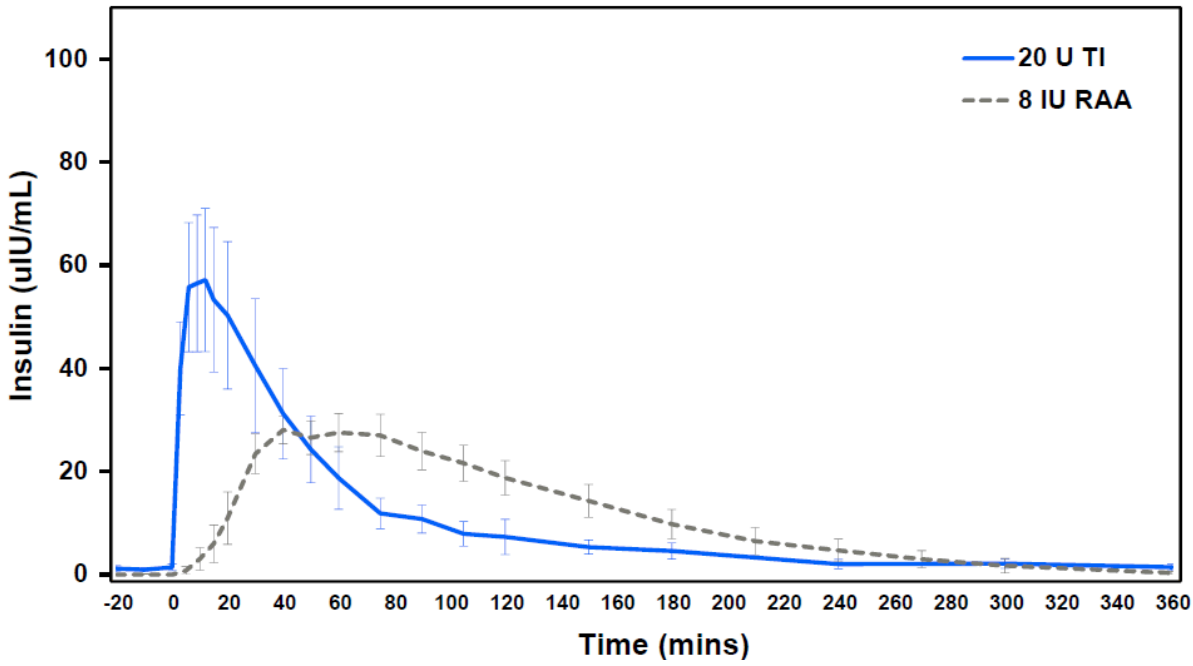
tolerated and toxicity is associated only with exaggerated insulin pharmacology (ie, hypoglycemia) at high doses in rodents and dogs; no target organ toxicities have been identified at multiples of the highest clinical doses. No proliferative changes (based on proliferating cell nuclear antigen [PCNA] staining) were noted in the lungs in a 104-week rat study or a 39-week dog study using the inhaled route of delivery. An extensive histopathologic examination of the respiratory tract from the nares to the alveoli was obtained in each pivotal inhalation study. No metaplasia was seen in any area of the respiratory tract. In the rat, goblet cell hyperplasia and some epithelial degeneration of the nasal cavities and bronchial cell proliferation were observed with TP alone, probably as a result of the impact of the very high dose (50 mg/kg/day) on the upper respiratory tract. TI and TP are neither mutagenic nor carcinogenic (in 104-week rat and 26-week rasH2 transgenic mice carcinogenicity studies) and have substantial safety margins (7-fold to 10-fold based on FDKP exposure) relative to the maximum proposed daily human dose.

Clinical Pharmacology

Pharmacokinetics (PK) and Pharmacodynamics (PD)

Characteristic features of insulin PK/PD after TI inhalation (rapid absorption/onset of action and relatively short duration of action) have been consistently demonstrated across all trials, independent of dose, inhaler, or subject population studied to date. Trials have demonstrated this unique PK/PD profile of TI when compared with that of RHI or RAA insulins. After inhalation of TI, absorption of insulin from the lungs into the blood stream is rapid with a median time (t_{max}) to maximum concentration (C_{max}) of 7.5 to 20 minutes, with most values in the 12 to 15 minute range. Insulin exposure (area under the curve through 180 minutes [AUC_{0-180}] and C_{max}) is dose proportional with intrasubject variation of 34% for AUC_{0-180}. Comparative PK between the Gen2 and MedTone inhalers (inhalation of 2 x 10 U Gen2 cartridges, 1 x 20 U Gen2 cartridge, and 1 x 30 U MedTone cartridge) results in superimposable insulin concentration-time curves. Insulin PK is similar in healthy volunteers and subjects with T1DM or T2DM, and no clinically significant drug-drug or drug-disease interactions have been noted, including in subjects with upper respiratory infection (URI), chronic obstructive pulmonary disease (COPD), or smokers. Insulin exposure in subjects with asthma who withheld their bronchodilator was 18% lower than when TI was administered 5 minutes after bronchodilator dosing.

Mean (SE) of Baseline-Corrected Insulin Concentration over Time (Trial 177)



Abbreviations: IU=international units; RAA=rapid-acting analogue (of insulin); SE=standard error; TI=Technosphere Insulin; U=units (fill content of TI cartridges).

TI has a more rapid onset of insulin action and shorter duration of effect, as measured by the glucose infusion rate (GIR) during a euglycemic clamp study, when compared with sc RHI or RAA insulin lispro. The baseline-corrected median GIR t_{max} for TI (53 minutes) occurred considerably earlier than with RHI (3 to 4 hours) or with the RAA comparator (108 minutes). A standard meal challenge demonstrated a significantly lower baseline-normalized postprandial glucose exposure with TI compared with RAA insulin, as well as a more rapid suppression of endogenous glucose production.

Following inhalation, TI is distributed uniformly throughout the lungs. Insulin pulmonary concentrations after TI inhalation demonstrated that <1% of the insulin remains in the lungs by 12 hours after administration. Concentrations of FDKP in the lungs follow a similar pattern. FDKP absorbed into the systemic circulation from the lungs is not metabolized and is eliminated via the renal route. The plasma PK profile of FDKP is characterized by a rapid rise in concentration and a short distribution period, without significant accumulation over a typical prandial dosing interval. Because FDKP is primarily cleared by the kidneys, diabetic subjects with moderate renal impairment exhibit a longer $t_{1/2}$ than those with mild or no renal impairment; C_{max} is unchanged. FDKP PK parameters are not significantly altered in diabetic subjects with mild to moderate hepatic impairment.

Converting from Subcutaneous Rapid Acting Analogs to Technosphere Insulin

The TI Inhalation System has been improved over the course of its development. Originally, TI was inhaled using the MedTone inhaler. This device was used in the earlier clinical trials submitted in the 2009 Original NDA. At that time, TI was filled in cartridges for the

MedTone inhaler in quantities of 15 U insulin (5 mg TI Inhalation Powder) and 30 U insulin (10 mg TI Inhalation Powder).

The MedTone inhaler was replaced by the Gen2 inhaler. The TI Inhalation Powder used in the Gen2 inhaler is the same as that used in the MedTone inhaler. However, because the Gen2 inhaler delivers the powder more efficiently than the MedTone inhaler, less powder is needed in each cartridge. For this reason, Gen2 cartridges contain 10 U insulin (3.3 mg TI Inhalation Powder) and 20 U insulin (6.7 mg TI Inhalation Powder).

Analyses of data from recently-completed clinical trials showed a 25% dose ratio between comparator sc insulin and TI. This is consistent with data from recent PK trials showing a bioavailability of 30% for TI compared with sc RHI and sc RAA. Taken as a whole, these data indicate that each TI Gen2 cartridge containing 10 U or 20 U of insulin approximates 3 units or 6 units of sc insulin, respectively.

The proposed Afrezza label uses these approximate insulin doses to transition patients from injected insulin to TI therapy, or to switch from TI back to injected insulin, if needed. Also, the approximate insulin dose is a reference point that enables the TI Gen2 cartridge to conform to traditional insulin units. Labeling the cartridge in this way gives patients, and prescribers, perspective for their initial inhaled TI dose relative to their experience with sc insulin.

Clinical Efficacy

Four Phase 3 trials across the spectrum of DM severity constitute the core of TI efficacy data: 2 trials with 883 T1DM subjects on a basal/bolus insulin regimen (Trials 171 and 009) and 2 trials with 971 T2DM subjects (insulin-naïve with inadequate glycemic control on OADs [Trial 175] or on prior insulin therapy [Trial 102]). The Gen2 inhaler was used in the recently-completed, pivotal Phase 3 trials (Trials 171 and 175). A head-to-head comparison between the Gen2 and MedTone inhalers in Trial 171 was used only to provide pulmonary safety bridging data. It was agreed with the FDA that the clinical trial efficacy results would be presented by trial (ie, not pooled).

All trials were randomized, controlled, multi-center, international trials with 24 (Trials 171 and 175) or 52 (Trials 009 and 102) weeks of treatment that compared TI with standard-of-care DM therapies or placebo. In the two T1DM trials, both active-comparator trials, each treatment group received basal insulin, and sc RAA insulin aspart was used as the prandial insulin comparator. The 2 trials in subjects with T2DM were placebo-controlled (Trial 175) or active-comparator (Trial 102) trials. Trial 175 compared the efficacy of TI or TP (Technosphere particles without insulin; ie, placebo) added to the pre-trial OAD regimen in insulin-naïve T2DM subjects. Prior to trial entry, these subjects were poorly controlled on metformin or 2 or more OADs (ie, their HbA1c was 7.5% to 10.0%) despite receiving maximum approved/maximum tolerated doses of OADs (metformin, dipeptidyl peptidase 4 [DPP-4] inhibitors, meglitinides or alpha-glucosidase inhibitors), or at least 50% of the maximum approved dose of sulfonylurea (SU). Trial 102 in insulin-treated T2DM subjects compared TI plus basal insulin to sc premixed biphasic RAA (BPR) 70/30 given twice daily (bid). Active-comparator trials were open-label, noninferiority trials; the double-blind, placebo-controlled trial was a superiority trial. For each of the 3 trials assessing primary

efficacy in terms of noninferiority, a margin of 0.4 was used. This noninferiority margin is consistent with the margin used in previous Phase 3 trials of FDA-approved prandial insulins and with guidance provided by the FDA.

The more recent pivotal Phase 3 trials in T1DM subjects (Trial 171) and T2DM subjects (Trial 175) utilized 4-week and 6-week run-in periods, respectively, during which time the subjects received nutritional and physical activity counseling, and training in the use of glucose meters, self-monitoring of blood glucose (SMBG), and electronic diaries. During the run-in period in Trial 171, all subjects were switched to or maintained on RAA insulin aspart as their prandial insulin. They continued with their pre-trial basal insulin (NPH, glargine, or detemir), which was titrated during this run-in period to achieve FPG between 100 mg/dL (5.6 mmol/L) and 120 mg/dL (6.7 mmol/L). Upon randomization, subjects in the TI treatment group were switched from insulin aspart to equivalent doses of TI; subjects randomized to the insulin aspart group continued their run-in insulin aspart therapy.

At randomization in the earlier trials (Trials 009 and 102), insulin-treated subjects were randomized to receive TI converted from their prandial sc insulin to TI using a 5-unit conversion factor (wherein 15 U TI MedTone cartridge approximates 5 units of sc RAA). This conservative conversion was considered appropriate, given the subjects' unfamiliarity with inhaled insulin titration, to ensure safe use. Based on this experience, and given that the inhaler used in the subsequent clinical program was the Gen2 inhaler, a 4-unit conversion factor was used for Trial 171 to determine TI starting doses. For the insulin-naïve subjects with T2DM in Trial 175, the starting dose of TI or TP (placebo) was 10 U with each meal. In all trials, following transition to TI (or TP), subsequent insulin dosing was individualized based on glucose values. In Trials 171 and 175, titration algorithms guided insulin dosing to meet pre-specified treatment goals based on 90-minute post-prandial blood glucose (BG) values (TI and TP) or pre-meal BG values (RAA comparator). Insulin titration was permitted for the first 12 weeks of the treatment period with a subsequent 12-week period of stable dosing.

The primary efficacy endpoint in all trials was the change in HbA1c from baseline to the end of treatment (Trials 171 and 175, week 24; Trials 009 and 102, week 52). Key secondary assessments included other glycemic endpoints (HbAlc goal attainment, fasting plasma glucose [FPG] change from baseline, and 7-point glucose profile), and weight changes. Hypoglycemia incidence and event rates were determined based on subjects' diary records, or if recorded as a Serious Adverse Event (SAE) when any SAE criterion was met. Hypoglycemia measures were generally regarded as safety endpoints in the individual trials. However, given that hypoglycemia occurs within the context of increasing insulin titration to achieve glycemic control, the hypoglycemia data are presented and discussed under efficacy.

The results of these clinical trials demonstrate that TI is effective in reducing HbA1c in a broad range of subjects with T1DM or T2DM (see table below). In subjects with T1DM, in a basal/bolus treatment regimen, TI was noninferior to insulin aspart in lowering HbA1c after 24 weeks of treatment (Trial 171; between-group treatment difference 0.19% with 95% confidence interval (CI) [0.02, 0.36]). A wide range of sensitivity analyses was conducted for Trial 171 to explore the impact of missing data; the findings were supportive of the findings from the primary analysis. A durable treatment effect was noted in Trial 009, although

noninferiority in HbA1c change from baseline to week 52 with a basal/bolus insulin regimen was not confirmed for TI compared with insulin aspart (upper limit of the 95% CI for the between-group difference was exactly 0.4%, with the pre-specified noninferiority criterion being strictly <0.4%).

Both T2DM trials met their primary efficacy endpoint. In insulin-naïve subjects with inadequate glycemic control on OADs, TI was superior to TP (placebo) in HbA1c reduction from baseline at 24 weeks (Trial 175; between-group treatment difference -0.40% with 95% CI [-0.57, -0.23] and p< 0.0001). In insulin-treated subjects with T2DM, TI plus basal insulin was noninferior to BPR 70/30 bid in HbA1c change from baseline at 52 weeks (Trial 102; between-group treatment difference 0.12% with 95% CI [-0.05, 0.29]).

HbA1c (%) Change from Baseline in T1DM and T2DM Trials (Primary Analyses)

Statistic	TI	Comparator	Treatment Difference TI - Comparator
T1DM			
Trial MKC-TI-171 Week 24			
Number of Subjects in FAS	174	170	--
Baseline HbA1c (%)	7.94	7.92	--
Adjusted Mean Change (SE), %	-0.21 (0.062)	-0.40 (0.060)	0.19 (0.086)
95% CI	(-0.33, -0.09)	(-0.52, -0.28)	(0.02, 0.36)*
Trial MKC-TI-009 Week 52			
Number of Subjects in the mITT population	277	262	--
Baseline HbA1c (%)	8.41	8.48	--
Adjusted Mean Change (SE), %	–0.13 (0.058)	–0.37 (0.059)	0.24 (0.082)
95% CI	(–0.24, –0.01)	(–0.49, -0.25)	(0.08, 0.40)
T2DM			
Trial MKC-TI-175 Week 24			
Number of Subjects in FAS	177	176	--
Baseline HbA1c (%)	8.25	8.27	--
Adjusted Mean Change (SE), %	-0.82 (0.061)	-0.42 (0.062)	-0.40 (0.087)
95% CI	--	--	(-0.57, -0.23)
p-value	--	--	< 0.0001*
Trial MKC-TI-102 Week 52			
Number of Subjects in the mITT population	302	316	--
Baseline HbA1c (%)	8.69	8.68	--
Adjusted Mean Change (SE), %	-0.59 (0.063)	-0.71 (0.061)	0.12 (0.085)
95% CI	(-0.71, -0.47)	(-0.83, -0.59)	(-0.05, 0.29)*

CI=confidence interval; mITT=modified intent-to-treat; SE=standard error

Comparator was insulin aspart in Trials 009 and 171. Comparator was inhaled placebo in Trial 175. Comparator was BPR 70/30 in Trial 102.

* Met pre-specified criteria for noninferiority (Trial 171 and Trial 102) or superiority (Trial 175).

In both T1DM and T2DM populations, secondary glycemic efficacy results were supportive of the primary efficacy HbA1c findings.

TI resulted in a modest but potentially meaningful weight advantage that was maintained over a 24 to 52-week period with little (T2DM subjects) or no (T1DM subjects) weight gain noted in TI-treated subjects.

In all 3 active-controlled trials, both T1DM and T2DM subjects on TI experienced less hypoglycemia across severity categories with severe hypoglycemia event rates reduced by a range of 20% to 65% in the trials. Clinically-relevant reductions in the incidence and event rates of hypoglycemia were noted across all HbA1c target levels, maintained throughout the duration of the treatment period, and remained when hypoglycemia rates were adjusted for attained HbA1c levels and reduction in HbA1c from baseline. Compared with TP (placebo), as expected, TI was associated with more hypoglycemia; however, when analyzed by background OAD use, TI subjects on metformin had hypoglycemic event rates that were not different from those seen in TP subjects on metformin and SU, a commonly used 2-drug combination therapy.

The Insulin Treatment Questionnaire (ITQ) was used to obtain feedback from subjects in Trial 171 regarding their experience with the TI Inhalation System with the Gen2 inhaler. Subjects' ratings of their experiences were consistently positive and remained so over the course of 24-weeks of use.

In Trial 171, the overall mean daily prandial insulin dose was 102.7 U for TI group and 25.5 units for the insulin aspart treatment group resulting in an aspart/TI dose ratio of 25%. Based on the results of this trial (that utilized a conversion factor of 10 U TI approximating 4 units sc RHI or RAA) and more recent bioavailability trials conducted using the Gen2 inhaler, a 3-unit conversion factor is proposed for use in the prescribing information. Patients will be informed that the 10 U cartridge delivers approximately 3 units of sc injected insulin (and is labeled as "3 units").

Clinical Safety

TI safety has been evaluated in approximately 6500 adult diabetics and healthy volunteers. Of these, 5505 were subjects with T1DM or T2DM who participated in the Phase 2/3 clinical trials with duration of exposure of >14 days; they constitute the 2013 Resubmission Safety Population (3017 exposed to TI, 290 to TP [placebo], and 2198 to active comparator treatments). Nearly 25% of the TI-treated subjects were treated for more than 12 months.

New data since the original 2009 NDA submission and the 2010 Amendment have shown no significant changes in the TI safety profile. TI administered with the Gen2 inhaler has the same safety and tolerability profile as TI administered with the MedTone inhaler. TI continues to be well-tolerated for the control of hyperglycemia in adult subjects with T1DM or T2DM. The adverse effects identified in the clinical program include some that would be expected with the use of insulin, such as hypoglycemia and insulin antibody formation, and others related to the pulmonary route of delivery, such as respiratory adverse events.

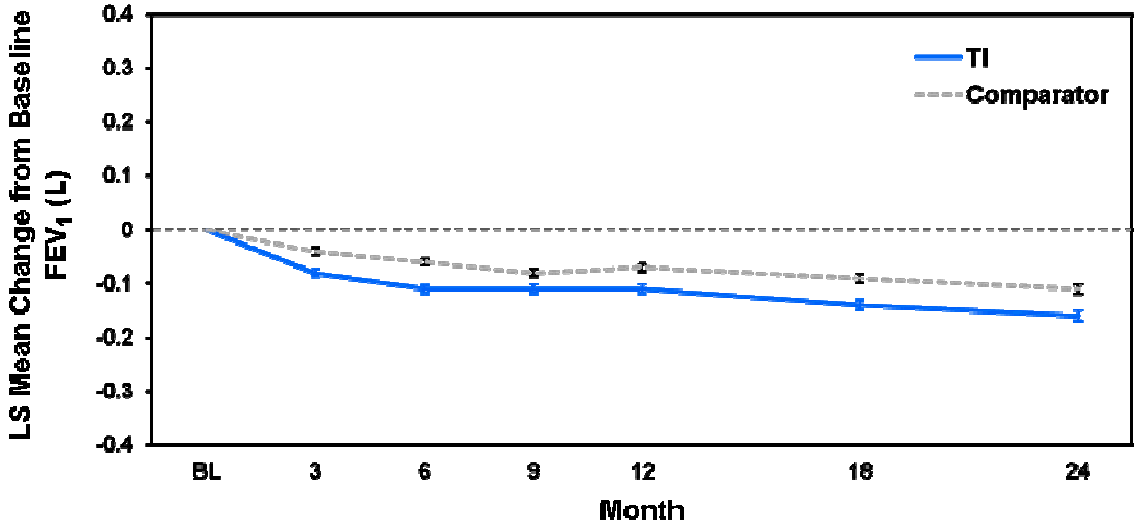
The incidence and severity of all treatment-emergent adverse events (TEAEs), excluding cough, were similar between the TI and comparator groups. Cough, reported more frequently with TI (~21% excess incidence versus comparators in the first week of use, declining to ~2% by the third month of treatment), was generally mild, transient, nonproductive, and occurred within 10 minutes of inhalation of the dry powder. There was no increase in deaths or serious adverse events (SAEs) in the TI treatment groups relative to the comparator groups. Ten (0.3%) TI-treated subjects and 7 (0.3%) comparator-treated subjects died. The most common treatment-related SAE was hypoglycemia (1.6%, TI group; 2.2%, comparator group). More TI subjects (7.2%) than comparator subjects (1.4%) discontinued trial participation due to AEs with cough being the most common TEAE that led to permanent early discontinuation.

The pulmonary safety of TI has been extensively characterized. Key pulmonary exclusion criteria for the Phase 2/3 trials included having active respiratory disease, a history of asthma or COPD, and/or significant radiologic or pulmonary function test (PFT) abnormalities. Current smoking was an exclusion criterion, but former smokers or those who stopped smoking at least 6 months prior were allowed to participate. All subjects enrolled in the clinical trials participated in a comprehensive pulmonary safety program that was rigorously conducted and monitored. Protocol-mandated PFTs were obtained at frequent, specified intervals in all trials; PFT analyses are based on nearly 34,000 tests. Only certified and trained pulmonary function laboratories that met the 2005 American Thoracic Society and/or European Respiratory Society pulmonary test performance and quality standards were utilized. All PFT tests were submitted for central, blinded review.

More TI subjects experienced respiratory TEAEs than subjects in the comparator group (45.2% versus 31.0%, respectively) with the difference due predominantly to cough. Dyspnea was uncommon, reported by 1.4% of subjects in the TI group, 0.7% in the TP group, and 0.3% in the comparator group. Other respiratory TEAEs of interest (asthma, wheezing, bronchospasm, bronchial hyperreactivity) were uncommon with incidence rates <1.0%. The incidence of respiratory SAEs were low for TI and the comparator groups.

PFT data from controlled efficacy and safety trials with treatment durations of at least 12 months were pooled and analyzed. Both TI and non-inhaled comparator groups showed small declines from baseline in mean forced expiratory volume in 1 second (FEV_1) over 24 months of continued treatment, with a greater initial decline (at month 3) noted in the TI group (treatment group difference in LS mean change from baseline was 0.04 L). Subsequently, the treatment group difference in mean change from baseline in FEV_1 remained fairly constant. The annual rate of change in FEV_1 was not statistically different between the groups, suggesting that the effect of TI on FEV_1 is small and non-progressive over 24 months of continued treatment. PFT treatment differences disappeared within 1 month of TI discontinuation.

LS Mean (SE) Change from Baseline in FEV_1 (Liters) by Visit using the MMRM Model for the Pooled Combined T1DM and T2DM PFT Population



Abbreviations: FEV_1=forced expiratory volume in 1 second; LS Mean=least square mean; MMRM=mixed model repeated measures; SE=standard error.

Long-term safety of TI in subjects with underlying lung disease such as asthma and COPD has not been established. In a small Phase 1 trial, 5 of 17 subjects with asthma who withheld their bronchodilator treatment developed bronchoconstriction, wheezing, and/or asthma exacerbation; 2 of these events were considered SAEs necessitating subject discontinuation from the trial. Serial spirometry before and after TI dosing showed a mean decrease in FEV_1 of ~12% that occurred within 15 minutes of TI administration; it resolved spontaneously over 120 minutes. In subjects with COPD, a ~9% mean acute decline of FEV_1 was noted on serial spirometry after a single dose of TI. Given these safety concerns, TI use will be contraindicated in people with asthma, COPD, or other chronic lung disease as per proposed product labeling.

There has not been an established causal association between long-term insulin use and cardiovascular (CV) risk. TI represents an alternate means of supplying insulin, but because it is not a distinctly different insulin molecule, there should be no new, distinct issues of CV risk with its use. TI clinical trials included in the safety analyses reported in the 2009 Original NDA were not designed to evaluate CV risks, and the trials did not selectively recruit high CV-risk subjects because a significant portion of the TI clinical development program had been completed before the FDA issued the 2008 guidance document concerning CV risk evaluation during new antidiabetic therapy development. For the 2013 Resubmission, CV analyses were conducted as agreed upon with FDA. No increased risk of CV or cerebrovascular events was noted with the use of TI in the combined population of subjects with T1DM or T2DM. CV relative risks, with 95% confidence intervals, were 0.96 (0.80, 1.14) using a broad analysis of CV TEAEs, and 0.58 (0.27, 1.26) using a custom CV TEAE analysis focusing on CV death, nonfatal myocardial infarction (MI), and nonfatal stroke. No clinically significant imbalance between TI and comparator groups was noted for specific CV events.

The incidence of malignant neoplasms (excluding non-melanoma skin cancers) was 0.43% (TI), 0.34% (TP), and 0.32% (active comparators) with no predominance of any specific type of cancer or clustering by organ system. Overall, the pattern was typical for the age group, consistent with the types of cancer most commonly observed in the diabetic population, and did not exceed the expected background incidence in the general US population. In the clinical program, 2 lung malignancies were diagnosed in TI-treated subjects: one in a controlled clinical study and one in an uncontrolled extension study. Both of these patients had a history of heavy smoking prior to entering the trials. No lung malignancies were reported in the comparator group.

The observed lung cancer incidence of 0.8 cases per 1,000 person-years in subjects treated with TI in clinical trials does not exceed the rate that would be expected among individuals with DM (1 to 2 cases per 1,000 person years).

Since completion of the trials, 2 voluntary reports of lung cancer cases were received, diagnosed 2.5 years and 3.5 years after having been treated with TI in the clinical trials. In the absence of a systematic follow-up, and given the lack of control group, information related to medical treatment or new risk factor exposure data since trial completion, it is difficult to ascertain causality. In addition, it is difficult to ascertain rates, as this very uncertain numerator is based only on voluntary reporting.

The incidence of benign neoplasms was comparable in the TI and active comparator groups. Radiologic findings of small lung nodules/cysts/opacities identified on serial HRCTs were reviewed and adjudicated by central, independent, blinded, radiologists; no new lung malignancies were identified in these subjects.

Development of anti-insulin antibodies (IABs) occurs with both recombinant human insulin and insulin analogs. In most large population trials, IABs have not been correlated with changes in efficacy or insulin dose requirements. Immunoglobulin G (IgG) IABs were measured consistently throughout the clinical program, and data were pooled at 3-, 6-, 12-, and 24-month time intervals for analysis. In subjects with T1DM, mean and median IAB levels increased from baseline by ~3-fold, returning towards normal within several months after therapy discontinuation. Minimal increases were noted in the comparator group. In both insulin-naïve and insulin-treated subjects with T2DM, minimal IAB increases were noted in the TI subjects. When compared with subjects receiving sc insulin, the median change from baseline in IAB concentrations in the pooled analysis was 1.8 versus 2.9 Kronus U/mL for TI and comparator groups, respectively. In the clinical impact analysis, no association was noted between IAB levels and clinical outcomes such as HbA1c, FPG, insulin dose, SAEs, and immunogenic TEAEs. No clinical consequences of elevated IAB levels were noted by analysis of absolute values, 95th percentile, or subjects with the highest IAB values.

The overall incidence of diabetic ketoacidosis (DKA) was 0.46% in the TI group and 0.23% in the comparator group. Early in the clinical development program, 2 long-term trials suggested an imbalance of DKA events in T1DM subjects, prompting careful ongoing surveillance. Most of these DKA events were related to concurrent infection and treatment interruption and/or reduced insulin dosing. With reinforced investigative site education, no new cases of DKA have been reported since the 2009 Original NDA.

There was no safety signal in the incidence, distribution, or severity of potentially immunogenic events reported with TI. The overall incidence of ophthalmic TEAEs was low and similar between the TI and comparator groups. There were no safety signals with regard to laboratory tests (excluding glucose), vital signs, or electrocardiograms (ECGs). Therapeutic (20 mg) and supratherapeutic (40 mg) doses of TP had no adverse QT/QTc effects.

Benefit-Risk Profile and Risk Management

AFREZZA provides diabetic patients and their HCPs a new therapeutic option in T1DM and T2DM management. It has been evaluated in clinical trials across a broad spectrum of diabetes severity (insulin-naïve subjects with T2DM, insulin-requiring T2DM subjects, and T1DM subjects utilizing a MDI basal/bolus regimen), in both open-label and placebo-controlled trials, and with active comparator agents representative of the current standard of care.

Clinical trial data demonstrate glycemic efficacy, reduced hypoglycemia, and weight neutrality. Convenience and ease of use that have been validated through clinical experience (inhaler treatment questionnaires) and human factor testing. Afrezza's unique PK/PD profile more closely mimics endogenous prandial insulin secretion compared with currently available RHI and RAAs. TI can benefit patients on basal/bolus insulin regimens who need simpler and more flexible prandial insulin meal/dose timing. Consistent with its time-action profile, a lowered postprandial hypoglycemia rate has been demonstrated in clinical trials. In addition, given the rapid kinetics of TI, supplemental prandial dosing is possible, if needed. Patients for whom weight and hypoglycemia are particular problems may find TI a useful treatment option. As it provides an alternative mode of insulin delivery, it may be helpful for patients with T2DM/T1DM for whom the injection process is a barrier to starting/maintaining insulin therapy. Subjects' ratings of their experiences with TI are consistently positive, including improved attitudes toward insulin therapy and high treatment satisfaction.

Specific risks highlighted for assessment due to the novel mode of administration (pulmonary) or because it is an insulin (hypoglycemia, antibodies) have been thoroughly evaluated. Cough, a common but transient adverse effect of dry powder inhalation, has not been associated with more adverse pulmonary consequences and can be managed with patient education. Labeling will state that patients using TI who experience persistent or recurring cough should be carefully evaluated, including spirometry as medically appropriate, to ensure that any underlying pulmonary pathology is detected in a timely manner. TI use will be contraindicated in patients with asthma, COPD, or chronic pulmonary disease. HCPs will be instructed that prior to initiating therapy with TI, all patients should be clinically evaluated with a detailed medical history, physical examination, and spirometry (FEV_1) to identify any potential underlying lung disease.

The incidence of lung cancer in subjects treated with TI in clinical trials is consistent with the rate expected in a diabetic population comprised of nonsmokers and ex-smokers. However, to evaluate the long-term risk of lung cancer, a postmarketing observational cohort trial is planned. The trial will provide additional quantification and characterization of potential

adverse events with low incidence or long latency after exposure to TI. In addition, the trial will help identify adverse events that may occur outside of the controlled clinical trial setting.

The risk management plan is summarized in the table below.

Overview of the Risk Management Plan

Proposed Label	REMS	Proposed Post-Approval Studies	Pharmacovigilance Plan
Contraindication: Patients with asthma, COPD, or other chronic lung conditions	**Communication Plan to inform HCPs of potential risk with TI** Screening for lung disease prior to starting TI • Lung function decline over time • Use by inappropriate patient populations (smokers, chronic lung disease)	Prospective, long-term, observational study to evaluate risk of: • Lung cancer • Other malignancies • Respiratory events • Hypoglycemia requiring medical interventions • Serious allergic events	Proactively identify, evaluate, and monitor targeted medical events such as respiratory events, malignancies, CV events, hypoglycemia requiring medical intervention, DKA, medication errors and product complaints, etc.
Warnings and Precautions: • Screening for potential lung disease before starting TI • Not recommended in smokers	**Additional voluntary measures outside of REMS** Instructions for Use Medication Guide Starter Kits		Signal detection and evaluation

COPD=chronic obstructive pulmonary disease; CV=cardiovascular; DKA=diabetic ketoacidosis; HCP=health care providers; REMS=Risk Evaluation and Mitigation Strategy.

TI, because of its unique PK/PD characteristics, glycemic efficacy, clinically-meaningful hypoglycemia and weight advantages, and its delivery of insulin in an alternative, noninvasive route of administration that provides convenience and ease of use, represents a useful addition to the therapeutic options available to patients and HCPs in the management of DM. Its safety profile is not associated with any clear safety signals, and potential risks will be better understood based on a comprehensive postmarketing surveillance program. With appropriate labeling of the product and the sponsor's commitment to identifying and implementing a broad risk management strategy, meaningful clinical benefits can be provided to patients. The favorable benefit/risk profile of TI justifies its use as an important additional therapeutic option for individualized DM management.

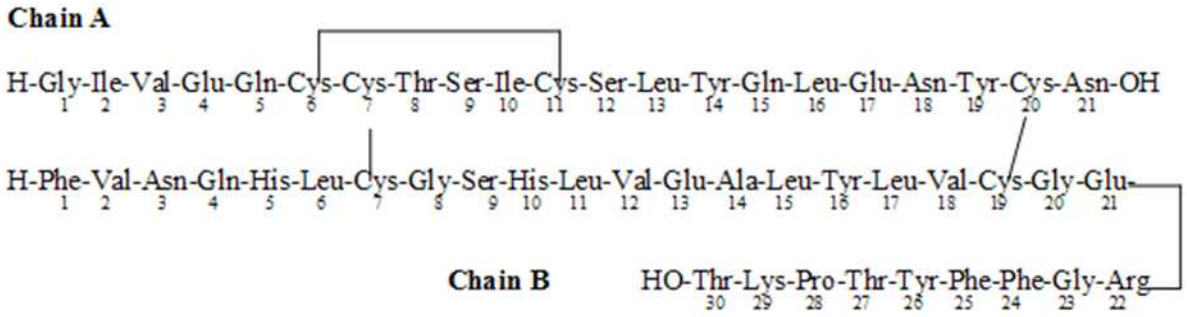
2 TECHNOSPHERE INSULIN INHALATION SYSTEM: DESCRIPTION AND PROPOSED INDICATIONS

TECHNOSPHERE® Insulin Inhalation System (AFREZZA®) is a combination drug/device product that was developed to address mealtime insulin needs in patients with diabetes mellitus (DM). It delivers insulin via a noninjectable, oral inhalation route. MKC is seeking approval (NDA 022472) for this indication:

- Afrezza is an ultra-rapid acting insulin indicated to improve glycemic control in adults with type 1 or type 2 diabetes mellitus (T1DM or T2DM)
    - For patients with type 1 diabetes, Afrezza should be used in regimens that include a long-acting insulin
    - Afrezza should not be used for the treatment of diabetic ketoacidosis (DKA)

Technosphere Insulin Inhalation Powder (hereafter referred to as TI Inhalation Powder or simply TI) is composed of recombinant human insulin (Figure 1), a novel excipient fumaryl diketopiperazine (FDKP), polysorbate 80, trace amounts of acetic acid, and water.

Figure 1: Insulin



Commercial TI will be packaged in pre-filled "3 unit" and "6 unit" cartridges approximating 3 and 6 units of subcutaneous (sc) insulin, respectively. It is administered using the Gen2 inhaler, a proprietary, breath-powered, dry powder inhaler designed for ease of use and consistent, reproducible insulin delivery.

When inhaled, TI has a more rapid onset of action and a shorter duration of action than either sc regular human insulin (RHI) or sc rapid-acting analog (RAA) insulins; its pharmacokinetic (PK) profile more closely mimics endogenous insulin mealtime secretion. TI is administered immediately before or within 20 minutes after starting a meal, as part of an individualized diabetes treatment regimen. It must be used with basal insulin in patients with T1DM and may be used with either oral anti-diabetic drugs (OADs) or basal insulin in patients with T2DM. It has been extensively evaluated in clinical trials in these populations.

3 BACKGROUND

3.1 Product Development Rationale

3.1.1 Disease Background

Diabetes mellitus is a chronic disease that is increasing in prevalence worldwide. In 2013 an estimated 382 million people were living with diabetes, half undiagnosed; 24.4 million were in the United States (US). The overall number is expected to increase to 592 million by 2035.[1] The rise in T2DM (accounting for approximately 90% to 95% of all cases of diabetes) parallels the rise globally in obesity.[2] The incidence of T1DM is also increasing, with continuous longitudinal 20-year data from the Philadelphia Pediatric Diabetes Registry demonstrating an estimated average yearly increase of 1.5%.[3]

Diabetes increases the risk of disabling and life-threatening long-term complications from microvascular and macrovascular disease and is a major cause of premature mortality. Approximately half of the people with T2DM die early from cardiovascular disease (CVD), and approximately 10% die of renal failure.[4] Mortality rates in people with T1DM, while improving, remain 7-fold higher than expected.[5] Given the current and predicted estimates for diabetes prevalence, prevention and control of diabetes and its societal health care burden are global priorities.

3.1.2 Diabetes Treatments and Treatment Goals

Effective diabetes treatment is critical in managing its long-term complications. Lowering glycosylated hemoglobin (HbA1c) levels to below or around 7% has been shown to reduce microvascular complications of diabetes and, if started soon after diagnosis, is associated with long-term reduction in macrovascular disease.[6,7,8,9] Thus, a reasonable HbA1c target is <7%. However, more (<6.5%) or less (<8.0%) stringent glycemic goals may be appropriate for some patients. Current treatment guidelines (Appendix 1) stress setting individualized patient treatment goals, dependent on many factors, including patient preferences.[10] In addition to targeting HbA1c goals, preprandial and peak postprandial glucose (PPG) targets have also been defined. Unfortunately, efforts to achieve near-normal blood glucose levels have been associated with a substantially increased risk of hypoglycemia (particularly in those with T1DM, but also noted in recent large T2DM trials).[10] Thus, severe or frequent hypoglycemia mandates modifying treatment regimens including setting less stringent glycemic goals.

In patients with T1DM, insulin-producing beta cells (β-cells) in the pancreas are destroyed through an autoimmune process usually leading to absolute insulin deficiency. They should be treated with a multiple-dose insulin (MDI) regimen, 3 to 4 injections per day of basal and prandial insulin or insulin pump therapy. Treatment guidelines recommend that patients match prandial insulin to carbohydrate intake, pre-meal blood glucose, and anticipated activity. For most patients (especially those with a history of hypoglycemia), use of insulin associated with less hypoglycemia (ie, insulin analogs) is recommended.[10]

T2DM is characterized by insulin resistance and progressive insulin deficiency. A very early defect, loss of the acute insulin secretory response to glucose, precedes and predicts diabetes.[11] Usually patients with T2DM are started on metformin as initial therapy. If target HbA1c goals are not achieved within 3 months of such noninsulin monotherapy at a maximal tolerated dose, a second oral agent, GLP-1 receptor agonist, or insulin should be added. Recent guidelines stress a patient-centric approach to therapy selection that takes into consideration efficacy, cost, potential side effects, weight changes, comorbidities, hypoglycemia risk, and patient preferences.[10] After approximately 3 months of two-drug combinations, if target HbA1c has not been reached, additional therapy is required. Not surprisingly, the most effective glycemic control will usually be obtained with insulin therapy, especially when the degree of hyperglycemia (eg, HbA1c ≥8.5%) makes it unlikely that another drug will be sufficiently effective. Ultimately, due to progressive β-cell dysfunction in T2DM, many patients, especially those with long-standing disease, will require and benefit from insulin therapy.

The principle of insulin use is creating as normal a glycemic profile as possible without unacceptable weight gain or hypoglycemia. Anticipated glucose lowering effects should be balanced with the convenience of the regimen.[12]

3.1.3 Obstacles to Effective Glycemic Control

Despite the importance of glycemic control and the availability of a range of therapeutic options, the majority of diabetic patients do not achieve recommended glycemic targets.[13] In T1DM patients, a number of psychosocial variables have been implicated as barriers to the adoption of intensive diabetes management strategies. Psychological and diabetes-specific distress, fear of hypoglycemia, concern about weight gain, and related eating disorder behaviors may lead patients with T1DM to restrict necessary insulin doses (ie, take less insulin than prescribed) or omit doses altogether.[14,15] Such behavior is relatively common, with intentional insulin restriction reported by 30% of women with T1DM, and results in poorer glycemic control, increased rates of acute and chronic complications, hospital admissions for diabetic ketoacidosis (DKA), increased risk for mortality, and shortened life span.[15,16,17] Assessment of attitudes and beliefs about insulin is important to improve glycemia and diabetes self-management.

For T2DM patients, overall tolerability issues associated with many available therapies (eg, weight gain, hypoglycemia, gastrointestinal side effects), especially when advancing to dual combination therapy, may limit dosing and reduce therapeutic benefit. Another impediment to effective diabetes control in T2DM patients has been termed “clinical inertia” (the lack of initiation or intensification of therapy when clinically indicated) which is most notable with insulin initiation.[18,19] The cross-national Diabetes Attitudes, Wishes, and Needs (DAWN) trial found that most nurses and general practitioners (50% to 55%) delay insulin therapy until absolutely necessary; delay was higher among US providers than in most other countries. This correlated with the more general reluctance to prescribe diabetes medication (or medication generally).[20] In an analysis conducted by a large integrated health care system, T2DM patients had a mean baseline HbA1c of 9.6% before starting insulin.[21] Two population-based analyses, 1 in the United Kingdom (UK)[22] and 1 in the US[23] found that on average patients delayed starting insulin for almost 5 years after failure of glycemic control

with oral anti-diabetic drugs (OADs). A recent assessment of glycemic control in a single institution found that 44% of T2DM patients with HbA1c >8.5% were not on insulin therapy.[24]

Patient barriers to effective use of insulin therapy exist among patients with T2DM as well. Among diabetes patients who use insulin, 57% omit insulin injections sometimes and 20% do it on a regular basis.[25] Multiple factors (including lifestyle, convenience, fear of needles/injections, and fear of weight gain) are associated with this behavior, with pain and embarrassment being the most prominent correlates with low insulin adherence in patients with T2DM in the DAWN trial.[20] Although advances in injection technology (eg, needle design and manufacture, insulin pens of increasing sophistication) have improved injection comfort and patient acceptance, insulin adherence remains suboptimal.[26,27] In a 2008 injection impact survey among adults with T1DM or T2DM, HCPs, endocrinologists, and certified diabetes educators, 36% of HCPs reported that patients are concerned about their insulin injections, and 33% of people with diabetes who use insulin injections dread their injections.[28]

Ultimately, however, hypoglycemia (and the fear of it) is the limiting factor in achieving glycemic control in patients with diabetes.[29, 30] It is the most frequent metabolic complication experienced by older adults in the US.[31] Even mild hypoglycemia may be inconvenient or frightening to people with diabetes. Eating more food causing weight gain is a common defensive measure. Severe hypoglycemia can cause acute harm to the person with diabetes or others, has been associated with increased subsequent mortality, and may affect cognitive performance.[32,33] The ADA Workgroup on Hypoglycemia has proposed that a significant reduction in the incidence of severe hypoglycemia (even by as little as 10% to 20%) or a ≥30% reduction in overall hypoglycemia incidence, event rates, or both by a new drug, device, or management strategy would represent a clinically important improvement over existing therapies.[34]

Given the barriers that limit effective glycemic control, such as clinical inertia in starting insulin, poor patient compliance with complicated insulin regimen, and fear of weight gain and hypoglycemia, there is a need for additional insulin therapies that could provide patients and HCPs with more options for individualized diabetes management.

3.1.4 Role of Technosphere Insulin in Diabetes Mellitus Treatment

The TI Inhalation System was developed to provide an ultra-rapid insulin for prandial glycemic management, one that closely mimics mealtime endogenous insulin secretion. As an inhaled formulation, TI is a painless, convenient, discrete, and non-invasive insulin treatment option that may be particularly useful for certain types of patients with T1DM or T2DM. Key features of pulmonary insulin absorption (a large absorptive area, good permeability and vascularization)[35] and the novel Technosphere technology result in very fast absorption of insulin into the bloodstream. This distinct pharmacokinetic (PK) and pharmacodynamic (PD) profile (rapid onset/relatively short duration) could offer benefit to patients on basal/bolus insulin regimen who need a simpler and more flexible prandial insulin meal/dose timing, especially if interprandial hypoglycemia is a problem. With TI, additional prandial dosing is possible if needed, helping to better treat persistently elevated mealtime

glycemic excursions. As less hypoglycemia and weight neutrality have been observed in clinical trials with TI, patients in whom weight and hypoglycemia are particular problems may find TI a helpful treatment option. In patients with visual impairment or loss of manual dexterity because of neuropathy, insulin dosing via simple cartridge insertion and use of inhaler may provide some advantages. Lastly, its convenience and ease of use may be particularly suitable for patients with T2DM/T1DM for whom the injection process is a barrier to starting/maintaining insulin therapy. However, since this is a novel route of administration, potential risks have been carefully addressed in the clinical program including PK characterization in special populations, pulmonary function testing in all patients, and long-term pulmonary safety surveillance.

3.2 Regulatory History and Clinical Development Program

The IND (061729) for this product was submitted to the United States (US) Food and Drug Administration (FDA) on 22 Dec 2000. On 16 March 2009, the 2009 Original NDA (022472) was submitted to FDA on the clinical efficacy and safety of TI delivered using the MedTone inhaler for the treatment of T1DM and T2DM in adult subjects.

The FDA response (Complete Response Letter [CRL], March 2010) cited inadequate titration of the drug product in the clinical trials and requested additional data to establish the clinical utility of TI in the treatment of DM. In addition, the FDA requested a human factors evaluation of the MedTone inhaler.

On 28 June 2010, MKC resubmitted the NDA (2010 Amendment) to the FDA. In this submission, MKC proposed to market the Gen2 inhaler (a new inhaler with re-designed TI cartridges). The Gen2 inhaler and cartridge were designed to provide equivalent insulin exposure to the MedTone inhaler, while providing greater ease of use. In vitro performance data and comparative PK data (Trial 142) were submitted to bridge the Gen2 inhaler to the Phase 3 trials that had been conducted with the MedTone inhaler.

On 18 January 2011, the FDA issued a second Complete Response Letter (CRL2). The FDA was concerned about a lack of meaningful information regarding the Gen2 inhaler related to subject use and its impact on efficacy and safety. The FDA requested that MKC conduct 2 randomized, controlled, Phase 3 clinical trials using the Gen2 inhaler in subjects with T1DM and T2DM. The Agency requested that the trials ensure adequate and appropriate titration of insulin with at least 12 weeks of relatively stable insulin dosing. The FDA specified that one of the trials needed to include the MedTone inhaler in addition to the Gen2 inhaler to allow for a head-to-head comparison of pulmonary safety data for the 2 devices. In addition, the FDA provided specific requirements for product labeling and requested a human factors evaluation of the Gen2 inhaler and Gen2 inhaler dose proportionality data.

To address the issues noted in the CRL2, and as agreed to by the FDA, MKC conducted the following trials and included them in the 2013 Resubmission:

- Two new phase 1 trials evaluating multiple-dose TI Gen2 administration (Trial 176) and comparing insulin exposure and response following administration of TI using the Gen2 inhaler versus sc RAA (Trial 177).

- Trial 176: A Phase 1, Open-label, Randomized, Crossover Design Clinical Trial in Healthy Normal Volunteers to Evaluate Insulin Exposure and Effect Following Inhalation of Technosphere® Insulin Inhalation Powder at Multiple Doses Using the Gen2C Inhaler

- Trial 177: A Phase 1, Single-center, Open-label, Randomized, Crossover Design Clinical Study in Subjects with Type 1 Diabetes to Compare Insulin Exposure and Response Following Inhalation of Technosphere® Insulin Inhalation Powder Using the Gen2C Inhaler Versus Subcutaneous Rapid-Acting Analog

- Two new pivotal Phase 3 trials

  - Trial 171: A Phase 3, Multicenter, Open-label, Randomized, Forced-titration Clinical Trial Evaluating the Efficacy and Safety of Technosphere® Insulin Inhalation Powder in Combination with a Basal Insulin Versus Insulin Aspart in Combination with a Basal Insulin in Subjects with Type 1 Diabetes Mellitus Over a 24-week Treatment Period

    - This trial included the head-to-head Gen2 vs MedTone comparison and served to bridge the safety data for TI Gen2 to the safety data obtained in the earlier trials done with the MedTone inhaler (Sections 4.4 and 9.5).

  - Trial 175: A Phase 3, Multicenter, Double-blind, Placebo-controlled, Randomized, Clinical Trial Evaluating the Efficacy and Safety of Prandial Technosphere® Insulin Inhalation Powder Versus Technosphere® Inhalation Powder (Placebo) in Insulin Naïve Subjects With Type 2 Diabetes Mellitus Poorly Controlled With Oral Antidiabetic Agents Over a 24-week Treatment Period

A comprehensive Gen2 device human factors evaluation addressed and mitigated the deficiencies identified by FDA in CRL2 (Section 4.2; Appendix 2).

In addition, the current submission provides pooled safety data from the 2 prior submissions and new data from 2013 for a safety assessment in 3017 diabetic (T1DM and T2DM combined) subjects treated with TI.

The regulatory timeline and key trials supporting the original NDA, the 2010 Amendment, and the 2013 Resubmission are described in Table 1 and depicted in Figure 2. Brief tabular summaries of all completed TI trials can be found in Appendix 3. Throughout the rest of the document clinical trial nomenclature has been abbreviated to Trial and the respective trial number.

Table 1: Regulatory Timeline with Key Trials

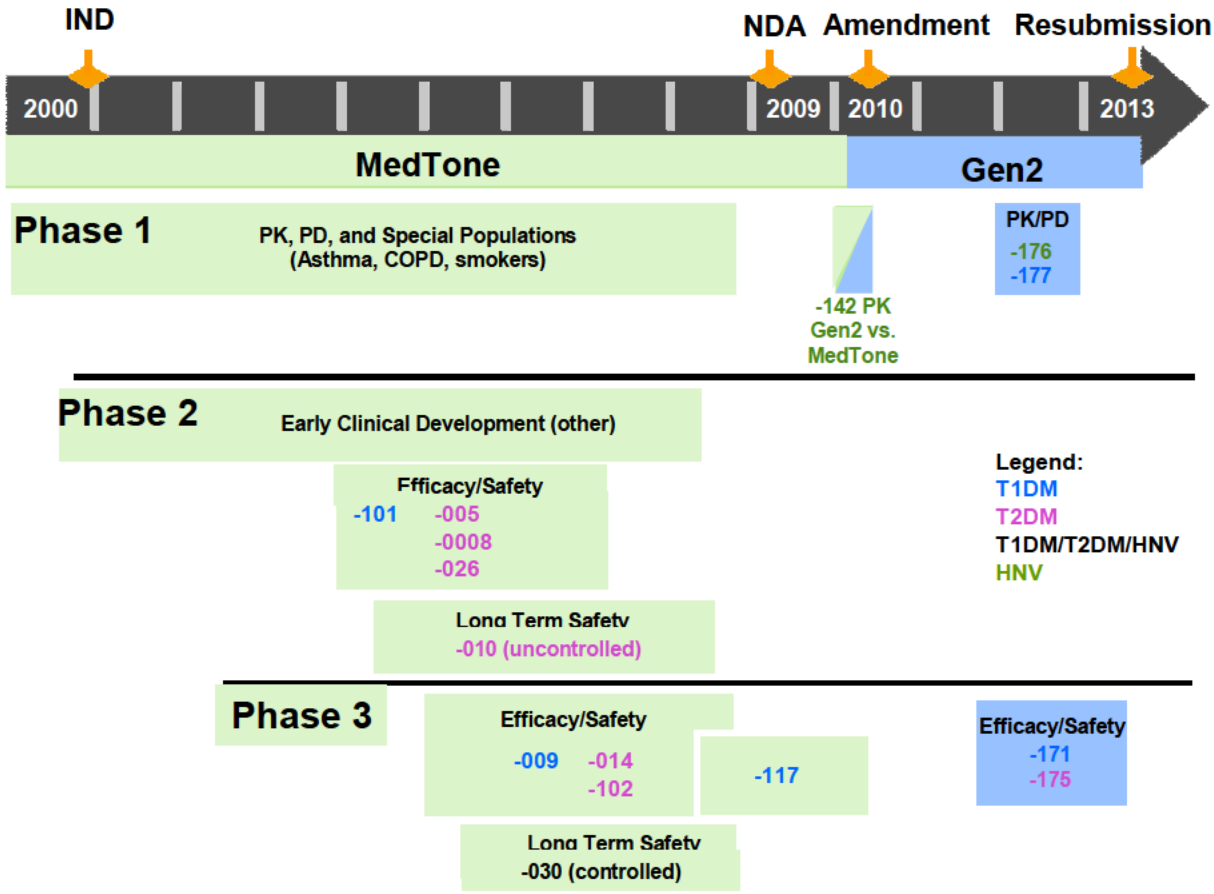
IND Dec 2000	**NDA Mar 2009 Trials in 2009 Original NDA**	**CRL1** Mar 2010	**Amendment Jun 2010 Trials in 2010 Amendment**	**CRL2** Jan 2011	**Re-submission Oct2013 Trials in 2013 Resubmission**
	HVs PDC-INS-0001, PDC-INS-0001A, PDC-INS-0002, PDC-INS-0007, MKC-TI-122 (pulmonary distribution) MKC-TI-015 (COPD) MKC-TI-113 (asthma) MKC-TI-114 (DDI) MKC-T-123 (mass balance) MKC-T-131 (QTc) T1DM PDC-INS-0011 (other) MKC-TI-025, MKC-TI-138,, MKC-TI-110, MKC-TI-116 (PK) MKC-TI-101 (Phase 2, safety and efficacy) MKC-TI-009 (Phase 3, safety and efficacy) T2DM PDC-INS-0003, PDC-INS-0003A, PDC-INS-0004A, MKC-TI-03B, MKC-TI-003B2 (PK/PD) MKC-TI-005 MKC-T-017 (renal) MKC-T-111 (hepatic) MKC-TI-016 (smokers) MKC-TI-027 (asthma) MKC-TI-118 (EGP) PDC-INS-0008, MKC-TI-026 (Phase 2, safety and efficacy) MKC-TI-010 (Phase 2, uncontrolled safety) MKC-TI-014, MKC-TI-102, MKC-TI-103, (Phase 3, safety and efficacy) T1DM and T2DM MKC-TI-030 (Phase 3, controlled safety) MKC-TI-112 (URI)		HVs MKC-TI-140, MKC-TI-141 (PK/ PD), MKC-TI-142 (PK) T1DM MKC-TI-117 (Phase 3, safety and efficacy) T2DM MKC-TI-118 (PK/PD)		HVs MKC-TI-176 (PK/PD) T1DM MKC-TI-171 (Phase 3, safety and efficacy) MKC-TI-177 (PK/PD) T2DM MKC-TI-175 (Phase 3, safety and efficacy)

Abbreviations: BE=bioequivalence; COPD=chronic obstructive pulmonary disease; CRL=complete response letter (from FDA); DDI=drug-drug interaction; EGP=endogenous glucose production; FDA=Food and Drug Administration (of the United States); HVs=healthy volunteers; IND=investigational new drug application; NDA=new drug application; PD=pharmacodynamics; PK=pharmacokinetics; RAA=rapid-acting analogue (of insulin); T1DM=type 1 diabetes mellitus; T2DM=type 2 diabetes mellitus; TI=Technosphere Insulin; URI=upper respiratory infection.

Inhaler type: All 2009 Original NDA trials (MedTone); 2010 Amendment (117 & 119 MedTone; 142 both; 134 Gen2); 2013 Resubmission (Gen2 except 171 [both]).

More details about these trials can be found in Appendix 3 and Appendix 5.

Figure 2: Regulatory Timeline with Key Trials



4 DRUG PRODUCT

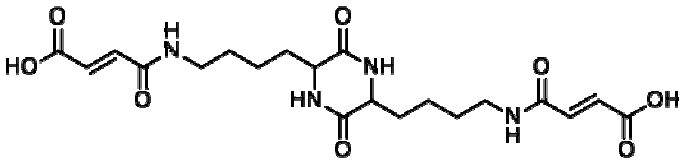
Afrezza Inhalation System is a drug/device combination product consisting of TI Inhalation Powder pre-filled into unit dose cartridges and the Gen2 inhaler. The cartridges contain human insulin produced by recombinant deoxyribonucleic acid (rDNA) technology utilizing a non-pathogenic laboratory strain of *Escherichia coli* (K12). Chemically, human insulin has the empirical formula $C_{257}H_{383}N_{65}O_{77}S_6$ and a molecular weight of 5808. Human insulin has the primary amino acid sequence shown in Figure 1 in Section 2.

Insulin is adsorbed onto carrier Technosphere particles whose formation is reproducible and well controlled without any sizing, milling, or blending required. The particle size is fixed before introduction of the active pharmaceutical ingredient (API). The carrier particles consist of FDKP (fumaryl diketopiperazine), polysorbate 80, and trace amounts of acetic acid and water. Each milligram of TI Inhalation Powder contains 3 units insulin.

FDKP is a novel excipient and the primary component of TI Inhalation Powder (Figure 3). It is biologically inert and forms the particle matrix of TI Inhalation Powder. TI Inhalation Powder is prepared by pH-controlled crystallization of FDKP. Insulin is subsequently adsorbed onto the surfaces of these particles to form TI Inhalation Powder. The low bulk

density, uniform particle size, and tight particle size distribution centered around 2 microns provide excellent aerodynamic properties that facilitate uniform distribution to the deep lung following inhalation.

Figure 3: Chemical Structure of FDKP



Upon inhalation, TI Inhalation Powder is evenly distributed throughout the deep lung where the particles dissolve readily (in approximately 7 seconds based on in vitro models) at prevailing physiological pH in lungs because FDKP is highly soluble at pH > 6.0.

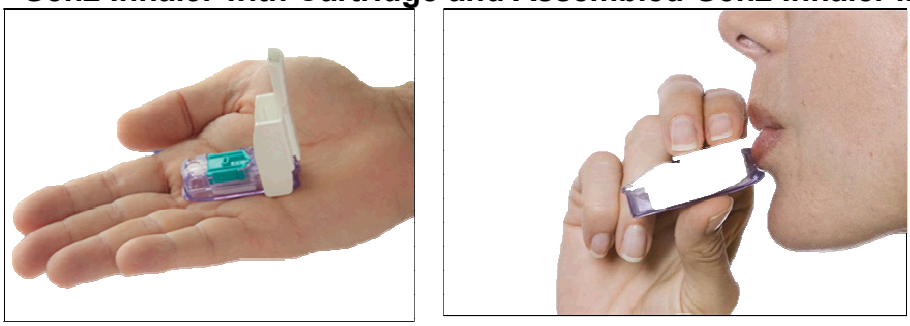
Once the particles are dissolved, both the FDKP and the insulin are absorbed passively and independent of each other. This rapid dissolution provides an insulin PK profile that mimics intravenous injection and results in an ultra-rapid onset of action. Absorption begins almost immediately after inhalation and circulating insulin and FDKP concentrations peak within minutes of administration. The absorbed FDKP is not metabolized and is excreted intact, primarily in the urine. The FDKP in the small fraction of swallowed powder is excreted intact in the feces. FDKP does not facilitate drug absorption, does not compromise the integrity of airway epithelial tight junctions or damage cell membranes but functions solely as the particle matrix to carry the insulin to the lung.[36] Insulin absorbed from the lungs avoids first pass metabolism in the liver.

Users self-administer TI Inhalation Powder by oral inhalation using the Gen2 inhaler (Figure 4). The system relies on the user's inhalation effort alone to produce a flow rate that delivers TI Inhalation Powder to the pulmonary tract. The to-be-marketed cartridges contain either 0.35 mg (10 U) or 0.7 mg (20 U) of insulin. The 10 U cartridge approximates 3 units of sc injected insulin (and is labeled as "3 units") and the 20 U cartridge approximates 6 units of sc injected insulin (and is labeled as "6 units"). Unless otherwise noted, TI cartridge units are described in terms of fill content throughout this document.

Refrigeration (5ºC ± 3ºC) is the recommended storage condition for TI Inhalation Powder. The proposed 24-month expiration date includes storage for up to 10 days at room temperature conditions during use.

The formulation for TI Inhalation Powder has been identical (unchanged) throughout the Phase 3 program regardless of inhaler device.

Figure 4: Gen2 Inhaler with Cartridge and Assembled Gen2 Inhaler in Use



4.1 Gen2 Inhaler

The Gen2 inhaler has been designed for use with TI cartridges. This device consists of custom, plastic, injection-molded components assembled with an ultrasonic weld. It is small/discrete and easy to use with low maintenance (discarded and replaced every 15 days). No cleaning is required. As a breath-powered inhaler, it relies on a person's inhalation effort to reproducibly deliver TI to the pulmonary tract.

Patient factors associated with the intended user population have guided the development of the TI Inhalation System. Early formative testing sessions using subjects with diabetes to evaluate system usage were informative and helped drive/reinforce the need for system simplicity. Subject conditions such as arthritis, neuropathy, retinopathy, and physical disability including amputation were considered. Ease of use is an essential aspect of the product and has therefore been validated through clinical experience (inhaler treatment questionnaires) and human factor testing.

Extensive testing, including monitoring of subject use in various clinical trials, shows that delivery of the powder occurs with inhalation efforts easily achieved by subjects. Over the course of the TI Inhalation System development program, human factors were considered to ensure the delivery system is aligned with user capabilities and can be used in a safe and effective manner. A Risk Analysis (ie, Failure Mode and Effects Analysis [FMEA]) was completed and identified various control measures for each potential failure mode. All of these risk management elements have since been evaluated and pertinent risk reduction actions have been incorporated. Usage tests were conducted on the Gen2 inhaler during the development program to incorporate subject-use aspects. These included an evaluation of subject inhalation effort, simulated-use trials, a survey of subject experience with clinical usage, inhaler returns testing, a pediatric usability trial, and formal usability tests.

Utilizing the approved test plan, with all FDA feedback incorporated, a comprehensive summative Human Factors Usability Validation Trial was conducted on the final to-be-marketed Gen2 TI Inhalation System. Sixty subjects with diabetes and 30 health-care providers (HCPs) were evaluated. Half of the participants were trained on proper use of the Gen2 TI Inhalation System and half were self-educated. In addition to normal dosing simulations, a set of high-risk use scenarios were investigated. The trial also included participants with neuropathy in their hands/arms (35%), retinopathy (58%), and color-blindness (25%). The results of the validation trial demonstrate that the TI Inhalation System

can be correctly, safely, and effectively used by the intended users (adults with T1DM or T2DM) and HCPs.

Additionally, the breath-powered mode of powder delivery has been similarly validated. Inhalation efforts achieved by subjects using the delivery system have been measured throughout the clinical program and shown to be sufficient for delivery of the inhalation powder.

4.2 Gen2 Inhaler Evaluation

Subject experience with the Gen2 inhaler was probed using an Insulin Treatment Questionnaire (ITQ) in clinical trials. During multicenter Trial 171, adult subjects with diabetes used the Gen2 inhaler for insulin treatment over a 24-week period. Periodically during the trial, subjects were asked to answer questions about their feelings and attitudes on the Gen2 inhaler. The subjects rated their experience positively; 88% of all answers were "agree" or "strongly agree". Attitudes and perceptions of the Gen2 inhaler remained positive and did not change over the course of 24 weeks of use. Additionally, Trial 159 was done specifically to examine in-use handling each Gen2 inhaler used for 15 days during the trial. The subjects in this trial also rated their experience with the Gen2 inhaler positively; 85% of all answers were "agree" or "strongly agree." Composite ITQ scores improved with continued use.

MKC completed a thorough evaluation of inhalers utilized in the clinical trials. A technical complaint system with 100% evaluation was established for the Gen2 inhaler per standard operating procedure. This product complaint reporting system allowed for identification of potential adverse events resulting from device failure and/or malfunction. Additionally, MKC tested 200 Gen2 inhalers returned from the Phase 3 clinical trials following the 15-day intended use period. The in vitro performance tests evaluated on these returned inhalers included assessments for defects, mechanical function, and powder delivery performance. Results did not reveal any deficiency or fault in the device and/or design. Additionally, rigorous life-cycle testing conducted by engineers at MKC further demonstrated the device to be capable of meeting its intended function over the in-use period.

More than 5,000 Gen2 inhalers have been dispensed to subjects in clinical trials. Seventeen device complaints were received. Only 1 of the complaints was confirmed to be an inhaler defect and was noted early in development. An adjustment to the inhaler that did not affect the flow path or powder performance was implemented to mitigate this before the start of the Phase 3 clinical trials, pivotal PK/PD trials, and the human factors summative validation trial. The other 16 complaints were confirmed to be associated with misuse (eg, shaking, stepping on device) or could not be confirmed as inhaler failures or defects; where appropriate, they were addressed by subject education efforts in the Instruction-for-Use (IFU). None of the complaints were associated with treatment-emergent adverse events (TEAEs).

In the 2013 Resubmission Safety Population, 370 subjects with either T1DM or T2DM received TI and 176 received placebo, both administered using the Gen2 inhaler. There were 10 (2.7%) subjects reporting a total of 13 device–related TEAEs (sinusitis, throat irritation, exertional dyspnea, upper-airway cough syndrome, and cough) using the Gen2 inhaler with

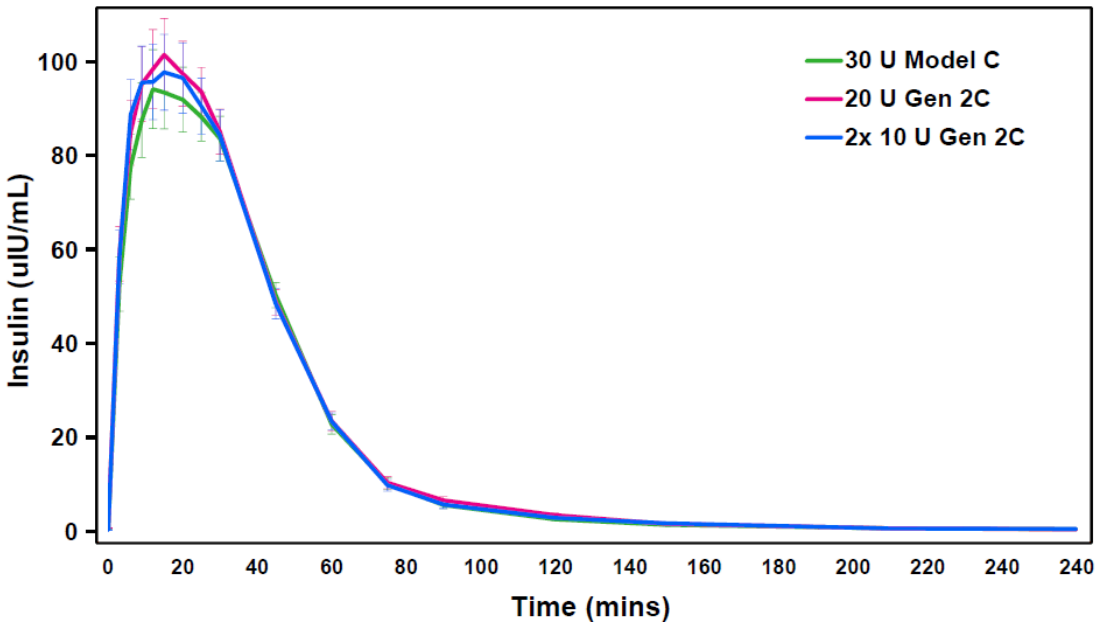
TI. There were 4 (2.3%) subjects reporting a total of 4 device-related TEAEs (all cough) using the Gen2 inhaler with placebo. After a careful review of all the data presented, MKC considered the TEAEs unlikely to be related to the Gen2 device.

4.3 Gen2 Inhaler Development History

The TI Inhalation System is a drug/device combination product for pulmonary insulin delivery consisting of TI (Inhalation Powder) pre-filled cartridges and the inhaler. During clinical development, the device has been improved to optimize performance. Both the earlier MedTone device and the proposed to-be-marketed Gen2 device were developed in incremental models. However, all Phase 3 trials used either the MedTone Model C device or the Gen2C device and will be referred to simply as MedTone and Gen2 in this document.

The initial device, the MedTone inhaler, was used in the clinical trials submitted in the 2009 Original NDA. In 2010, MKC switched developmental efforts from the MedTone inhaler to the Gen2 inhaler because of its notable advantages. While both inhalers are breath-powered and reusable, the Gen2 inhaler is smaller, has fewer parts, requires fewer steps for use, and needs only one inhalation per cartridge. The Gen2 inhaler is more efficient than the MedTone inhaler with 33% less TI needed to provide the same insulin exposure. Equivalence of 20 U and 30 U of TI delivered by Gen2 and MedTone inhalers, respectively, has been demonstrated ($AUC_{0\text{-}120}$ point estimate 1.060 [CI 0.981-1.145] and C_{max} 1.082 [CI 0.992-1.180]). Dose-equivalence between two 10 U TI Gen2 cartridges and one 20 U TI Gen2 cartridge was also demonstrated ($AUC_{0\text{-}120}$ point estimate 0.957 [CI 0.886-1.035] and C_{max} 0.930 [CI 0.852-1.014]) (Figure 5). These meet the BE criteria of 0.80 – 1.25.

Figure 5: Mean C-peptide-corrected Insulin Concentration-Time Profiles: 2 × 10 U Gen2, 1 × 20 U Gen2, and 1 × 30 U MedTone (Trial 142)



Abbreviations: Model C=MedTone inhaler; Gen 2C=Gen2 inhaler; uIU=micro international units; U=units (fill content of TI cartridges). Error bars=standard error.

4.4 Safety Bridging Between the Gen2 and MedTone Inhalers

As requested by the FDA (Section 3.2), a head-to-head comparison between the Gen2 and MedTone inhalers was performed in T1DM subjects (Trial 171) to provide sufficient data for bridging pulmonary safety data of recent trials conducted with the Gen2 inhaler with the extensive Phase 3 pulmonary safety data obtained with the MedTone inhaler. Comparable pulmonary function test (PFT) results over 24 weeks and similar overall pulmonary safety profiles were noted between TI Gen2 and TI MedTone treatment groups (Section 9.5).

5 NONCLINICAL DEVELOPMENT

A comprehensive evaluation of TI has been done to support long-term use in humans. Insulin has been in clinical use for diabetes treatment for decades; therefore, the nonclinical program consisted of evaluating the pharmacokinetics (PK), pharmacodynamics (PD), and safety of TI (insulin-adhered Technosphere particles) and Technosphere particles (TP) alone administered primarily by the pulmonary route. TI Inhalation Powder particles are inhaled into the lungs, where they dissolve immediately (approximately 7 seconds based on in vitro models) because FDKP is highly soluble at physiological pH. Once the particles are dissolved, both the FDKP and the insulin are absorbed passively and independently of each other.

This program provides full characterization of the potential adverse effects of both TI and TP (placebo, no insulin) on the respiratory system as well as the systemic effects of TP. The nonclinical development program is summarized in Table 2.

Table 2: Nonclinical Studies Performed with TI and TP

Study Type	Number of Tests TI	Number of Tests TP
Safety pharmacology	6	5
PK/ADME	10	14
Single-dose and repeat-dose toxicology	6	14
Genotoxicity	2	3
Carcinogenicity[a]	2	2
Reproductive and Developmental Toxicology	0	6

Abbreviations: ADME=absorption, distribution, metabolism, and excretion; PK=pharmacokinetics; TI=Technosphere Insulin; TP=Technosphere particles (placebo, no insulin).
a: There were 2 nonclinical carcinogenicity studies; both studies included both TI and TP.

Both high and low doses of TI and TP and an air control were administered to rats for up to 104 weeks by the inhalation route to assess carcinogenicity. There were no differences in mortality or survival across groups and no effect of either TP or TI on the incidence, distribution, number, or character of tumors. There was no increase in proliferating cell nuclear antigen (PCNA) labeling in the lung. Non-neoplastic nasal cavity lesions (goblet cell hyperplasia/eosinophilic droplet accumulation) were considered to be non-specific adaptive responses to chronic inhalation of particles.

A 26-week carcinogenicity study in rasH2 transgenic mice was performed by the subcutaneous route using 2 negative control groups, 2 TP and 2 TI groups, and a positive

control. The ras mouse carries 3 copies of the human prototype c-Ha-ras oncogene with its endogenous promoter and enhancer included in the construct which makes this model sensitive for detecting carcinogenicity. Additionally, this model shows a higher incidence of lung tumors such as lung alveolar epithelial tumors and lung adenomas. There was no evidence of carcinogenicity with either TI or TP in this study.

Based on the results of the studies enumerated in Table 2, the following conclusions were reached:

- Neither TI nor TP affects cardiovascular (CV), respiratory, central nervous system (CNS), or renal function in animals.
- Consistent with clinical data, after TI inhalation in rats and dogs, both insulin and FDKP are rapidly absorbed into the bloodstream. FDKP is not metabolized and is excreted unchanged, primarily in the urine.
- TI and TP are well tolerated and toxicity is associated only with exaggerated insulin pharmacology (ie, hypoglycemia) at high doses in rodents and dogs.
  - In all repeat-dose toxicology studies, the primary effects of TI were due to the pharmacologic effects of high insulin doses and no target organ toxicities were identified.
  - In rat and rabbit studies using sc TP, there was no impairment of fertility, teratogenic finding, or effect on offspring related to TP.
  - The cytotoxicity of both TI and TP was investigated in vitro in mouse 3T3 fibroblasts at concentrations ranging from 10 to 1000 mg/L. No cytotoxicity was observed.
  - TI and TP were administered to rats and dogs by the inhalation route for up to 104 and 39 weeks, respectively. An extensive histopathologic examination of the respiratory tract from the nares to the alveoli was obtained in each pivotal inhalation study. No metaplasia was seen in any area of the respiratory tract. In the rat, goblet cell hyperplasia and some epithelial degeneration of the nasal cavities and bronchial cell proliferation were observed with TP alone, probably as a result of the impact of the very high dose (50 mg/kg/day) on the upper respiratory tract.
  - No proliferative changes (based on PCNA staining) were noted in the lungs in a 104-week rat study or a 39-week dog study using the inhaled route of delivery.
- TI was studied in several genotoxicity studies (Ames test, chromosomal aberration assay, and mouse micronucleus test) and 2 carcinogenicity studies. TI and TP are neither mutagenic nor carcinogenic and have substantial safety margins (7-fold to 10-fold based on FDKP exposure) relative to the maximum proposed daily human dose.

In summary, no unexpected safety signals have emerged with TI and TP in an extensive nonclinical program.

6 CLINICAL PHARMACOLOGY

The key features of the insulin PK after TI inhalation (rapid absorption and relatively short duration) that make its time-action profile similar to endogenous prandial insulin secretion have been consistently demonstrated throughout the clinical pharmacology program, regardless of inhaler. Equivalence of the Gen2 and MedTone inhalers was demonstrated in

Trial 142. Trial 176 and Trial 177, utilizing the Gen2 inhaler, demonstrated dose-proportionality and unique PK/PD characteristics compared with not only regular human insulin (RHI) but also the rapid-acting analog (RAA) insulin lispro.

After inhalation of TI, absorption of insulin from the lung into the blood stream is rapid. Time (t_{max}) to maximum concentration (C_{max}) is typically 12 to 15 minutes with dose-proportional increases in exposure. Insulin concentrations return to baseline by 180 minutes. The distribution, metabolism, and elimination of insulin in plasma are well established and are not altered by delivering it via inhalation.

6.1 Overview

The relevant clinical pharmacology program in the 2013 Resubmission included extensive evaluation of PK/PD and bioavailability (BA)/BE of TI and/or TP in 31 trials conducted in healthy subjects; subjects with T1DM and those with T2DM; T1DM and T2DM subjects with upper respiratory infections (URIs); T2DM subjects with renal impairment, hepatic impairment, smoking habit, or asthma; and non-diabetic subjects with asthma or chronic obstructive pulmonary disease (COPD). A brief summary of clinical pharmacology trials is presented in Appendix 3.

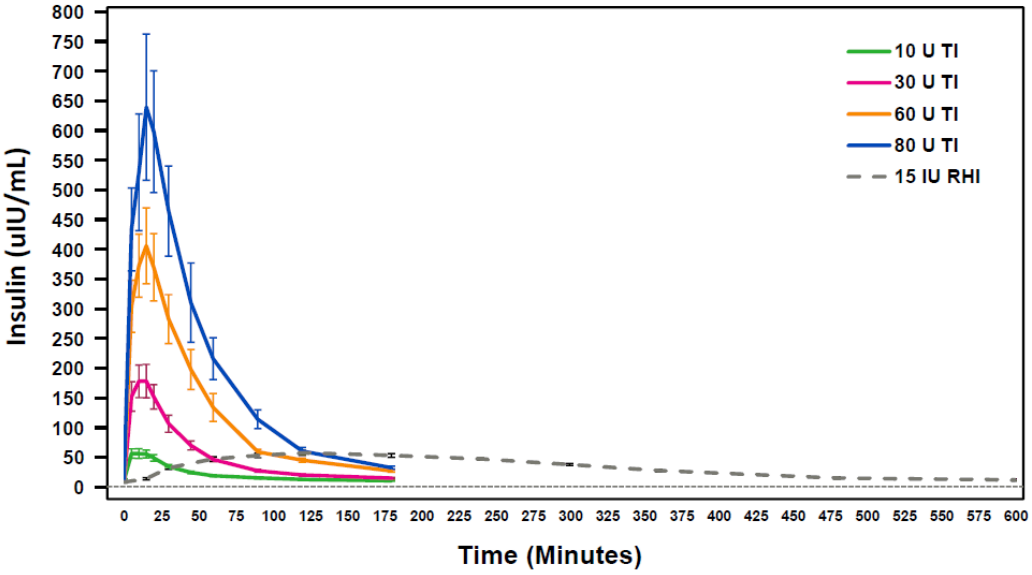
6.2 Insulin Pharmacokinetics

The plasma insulin concentration-time profiles after TI administered with the Gen2 inhaler (TI Gen2) in doses ranging from 10 U to 80 U compared with that seen after administration of 15 units sc RHI in Trial 176 are shown in Figure 6. Table 3 depicts the associated exposure parameters (C_{max} and area under the curve through 180 minutes [AUC_{0-180}]) for the TI doses administered. Consistent with earlier data obtained using the MedTone and Gen2 inhalers, insulin exposure (AUC_{0-180} and C_{max}) was dose proportional with intrasubject variation of 34% for AUC_{0-180}. Following TI administration, median t_{max} for insulin was 12 to 15 minutes in contrast to the t_{max} of approximately 120 minutes noted after sc RHI administration. Insulin concentrations returned to near-baseline by 180 minutes after TI inhalation compared to a duration of exposure >6 hours noted after sc RHI administration (Figure 6).

The t_{max} of insulin following TI inhalation has been consistent across all trials (median of 7.5 to 20 minutes, with most values in the 12 to 15 minute range) independent of dose, inhaler or subject population studied to date. The terminal half-life ($t_{1/2}$) of insulin was not tracked across trials because it is difficult to isolate the contribution of endogenous insulin from that of exogenously administered TI.

All available sc RAA insulins have modifications of one or more amino acids in the insulin molecule, and these changes to the insulin structure result in faster sc absorption compared with RHI. In Trial 177, the insulin concentration-time curves following administration of TI Gen2 and sc RAA insulin lispro were compared (Figure 7). The unmodified human insulin in TI was absorbed more rapidly (earlier t_{max}) and had a shorter exposure duration than the sc RAA.

Figure 6: Mean (SE) C-Peptide-Corrected Insulin Concentration-Time Profiles in Trial 176 Conducted with the Gen2 Inhaler



Abbreviations: IU=international units; RHI=regular human insulin; SE=standard error; TI=Technosphere Insulin; U=units (fill content of TI cartridges).

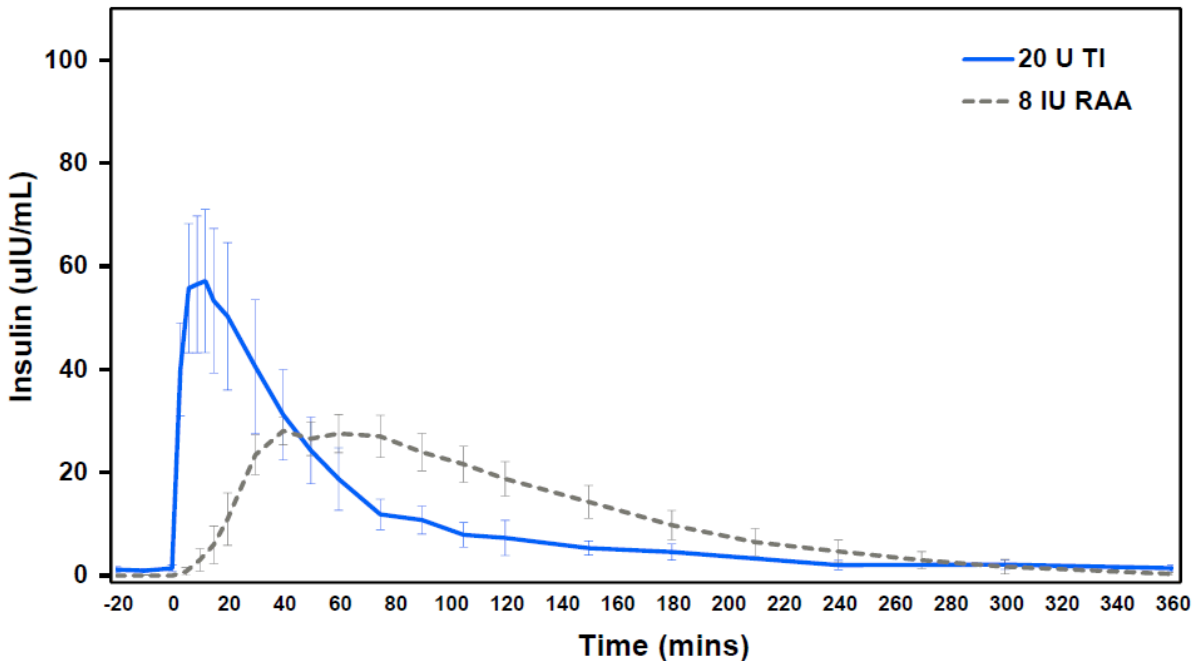
Table 3: Dose Proportionality Analysis of Insulin Based on C-Peptide Corrected RIA Assay (Trial 176)

Parameter	10 U TI (N=32)	30 U TI (N=32)	60 U TI (N=32)	80 U TI (N=32)	Slope (90% CI)[a]
$AUC_{(0-180)}$ (min·µIU/mL)					
Mean	3863.2	9325.4	22424.3	34893.6	
Geometric Mean	3416.52	8161.34	19015.68	27608.14	1.000 (0.939, 1.061)
SD	1634.31	5693.38	16294.82	31258.28	
%CV	42.3	61.1	72.7	89.6	
C_{max} (µIU/mL)					
Mean	63.3	187.8	444.3	681.5	
Geometric Mean	53.82	149.80	350.23	494.38	1.067 (1.013, 1.120)
SD	44.24	156.40	361.79	704.66	
%CV	69.9	83.3	81.4	103.4	

Abbreviations: AUC_{0-180}=area under the curve from time 0 to 180 minutes; CI=confidence interval; C_{max}=maximum concentration; %CV=percent coefficient of variation; IU=international units; RIA=radioimmunoassay; SD=standard deviation; TI=Technosphere Insulin; U=units (fill content for TI cartridges).

a: From power model: log(parameter) = period + log(dose) + subject; where subject is a random effect and dose is a continuous effect with compound symmetry variance/covariance matrix. Dose proportionality is achieved if the confidence limits are between 0.893 and 1.107.

Figure 7: Mean (SE) Baseline-Corrected Insulin Concentration-Time Profiles in Trial 177 Conducted with the Gen2 Inhaler



Abbreviations: IU=international units; RAA=rapid-acting analogue (of insulin); SE=standard error; TI=Technosphere Insulin; U=units (fill content of TI cartridges).

Trial 142 was conducted to show comparative PK between the Gen2 and MedTone inhalers. Inhalation of 2 x 10 U Gen2 cartridges, 1 x 20 U Gen2 cartridge, and 1 x 30 U MedTone cartridge resulted in superimposable insulin concentration-time curves (Section 4.3, Figure 5).

Relative BA for TI using the Gen2 inhaler has been evaluated in two recent trials. Against 15 U sc RHI, the median relative BA was 24% with a range of 20% to 27% for doses ranging from 10 U to 80 U TI (Trial 176). The relative BA of 20 U TI was 33% against 8 units sc RAA (Trial 177). The relative BA reported previously when using the MedTone inhaler ranged from 14% to 27%. The higher relative BA from the new trials is consistent with the more efficient delivery of powder by the Gen2 inhaler.

Insulin PK was similar in healthy volunteers and subjects with T1DM or T2DM. In addition, there were no clinically significant drug-drug or drug-disease interactions with inhaled bronchodilators (albuterol) and corticosteroids (fluticasone), COPD, URI, smoking, and asthma (on bronchodilator). Insulin exposure in subjects with asthma who withheld their bronchodilator was 18% lower than when TI was administered 5 minutes after bronchodilator dosing (Trial 131). The PK profile of insulin measured by $AUC_{0\text{-}4h}$ or t_{max} after dosing with TI after a meal challenge was similar during an active symptomatic URI compared with that seen after URI resolution (Trial 112). In contrast with data reported for other inhaled insulins where differences in insulin PK were seen between the 2 populations,[37,38,39] smokers and nonsmokers had similar PK parameters for insulin after TI administration (Trial 016).

6.3 FDKP Pharmacokinetics

FDKP absorbed into the systemic circulation from the lungs is not metabolized and is eliminated through the renal route (mass balance and metabolite profiling in Trial 123). The negligible amount of FDKP deposited in the throat and subsequently swallowed after TI inhalation is not absorbed. The FDKP plasma concentration-time profile has been consistent across all trials and is similar to that of insulin. Its plasma PK profile is characterized by a rapid rise in FDKP concentration (typical t_{max} is 10 minutes), a short distribution period, and a terminal half-life ($t_{1/2}$) ranging from 114 minutes to 198 minutes with no significant accumulation over a typical prandial dosing interval. FDKP exposure is dose proportional. The dose-normalized C_{max} is not significantly different across populations including subjects with renal impairment. Because FDKP is primarily cleared by the kidneys, diabetic subjects with moderate impairment exhibit a longer $t_{1/2}$ (270 min) than those with mild or no renal impairment (Trial 017). FDKP PK parameters are not significantly altered in diabetic subjects with mild to moderate hepatic impairment (Trial 111); subjects who smoke (Trial 016); or before or after an URI (Trial 112).

6.4 Insulin and FDKP Concentrations in the Lung

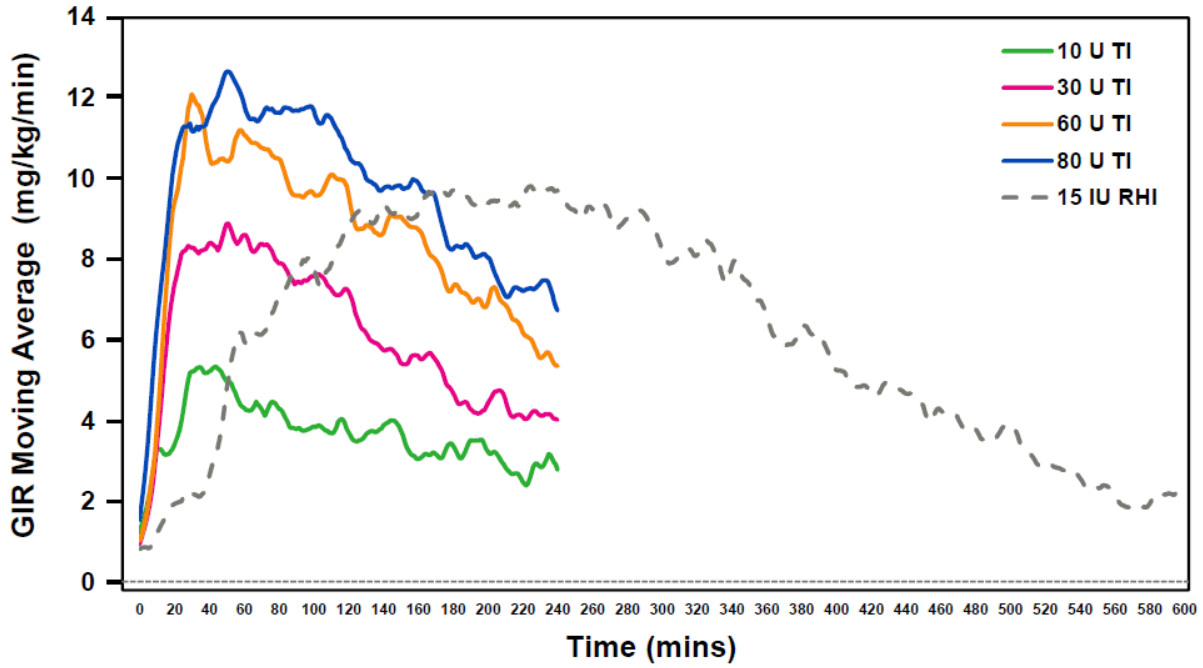
Following inhalation, TI is distributed uniformly throughout the lungs (Trial PDC-INS-0007). A serial assessment (using bronchoscopy with bronchoalveolar lavage [BAL]) of insulin pulmonary concentrations after TI inhalation (Trial 122) has demonstrated that <1% of the insulin remains in the lungs by 12 hours after administration, with the concentration of insulin in the BAL fluid near the assay detection limit (2 μU/mL). Concentrations of FDKP in the lungs follow a similar pattern.

6.5 Insulin Pharmacodynamics

Reduction in blood glucose (BG) concentration by insulin is quantified through euglycemic clamp techniques in which glucose and low-dose insulin are infused to suppress endogenous insulin secretion and hepatic glucose release, and to stabilize BG concentrations. The test article is then administered and glucose is infused at a variable rate to maintain a constant BG. The glucose infusion rate (GIR) represents the instantaneous demand for glucose and the area under the GIR-time curve (GIR AUC) represents the total glucose demand. Euglycemic clamp methodology is further described in Appendix 4.

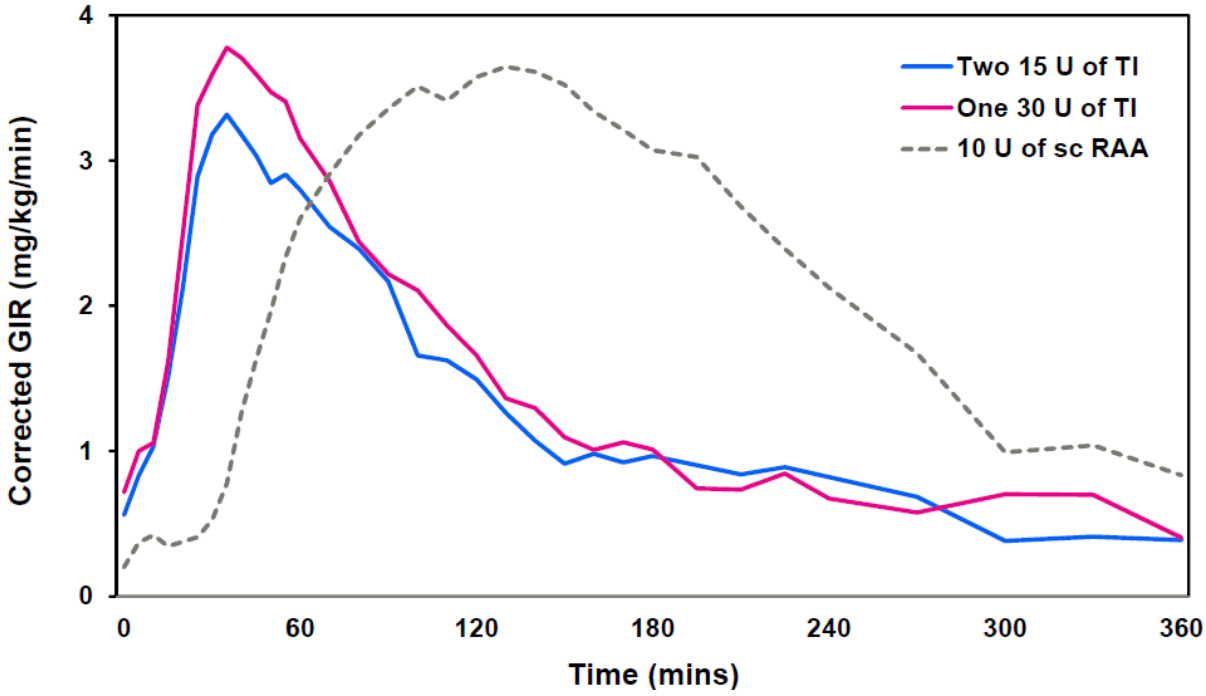
In Trial 176 using the Gen2 inhaler, increasing the dose of TI increased the observed peak in GIR (GIR_{max}) closer to its maximum value (E_{max}) and produced a longer duration of action (Figure 8). As shown previously (Figure 6), insulin exposure (insulin concentration-time curve AUC) from 60 U TI administered with the Gen2 inhaler is similar to that of 15 units sc RHI. However, while GIR t_{max} occurred within an hour after TI dosing and was greatly reduced by 180 minutes after dosing, the GIR t_{max} occurred 3 to 4 hours after sc RHI and the effect persisted beyond the normal postprandial time period (Figure 8). Similarly, a more rapid onset of insulin action and shorter duration of peak effect, as measured by the GIR, was also demonstrated for TI (MedTone inhaler in Trial 116) compared with sc RAA insulin lispro (Figure 9).

Figure 8: Mean Baseline-Corrected Glucose Infusion Rate (Trial 176)



Abbreviations: GIR=glucose infusion rate; IU=international units; RHI=regular human insulin; TI=Technosphere Insulin; U=units (fill content of TI cartridges).

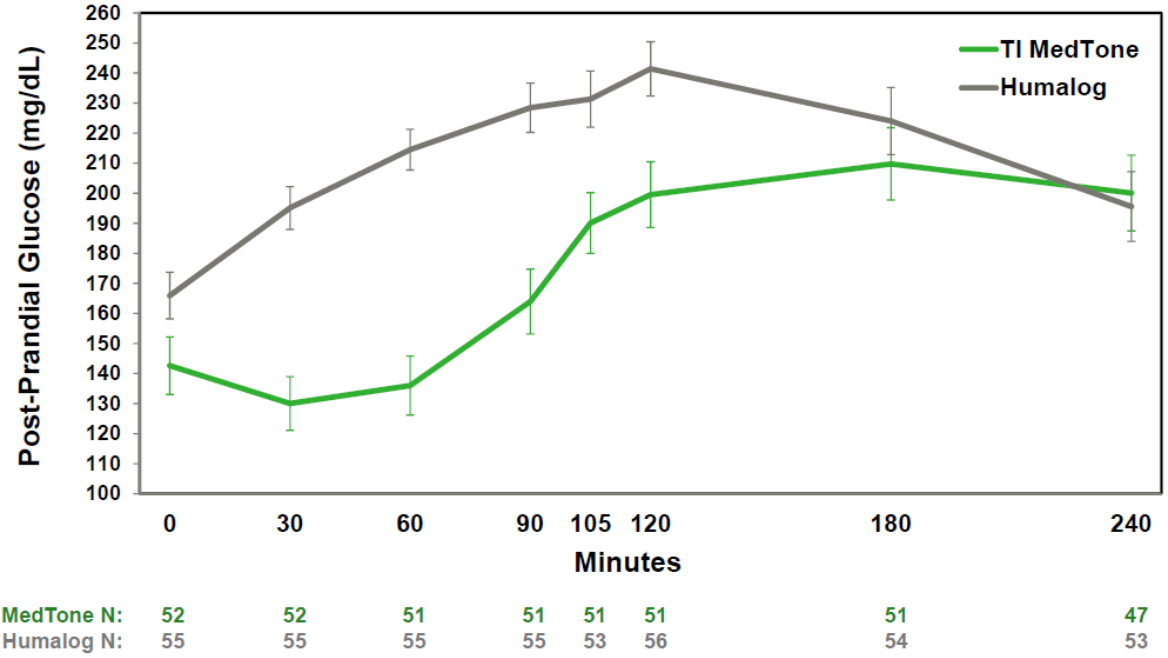
Figure 9: Mean Baseline-Corrected Glucose Infusion Rate (Trial 116)



Abbreviations: GIR=glucose infusion rate; RAA=rapid-acting analogue (insulin lispro); sc=subcutaneous; TI=Technosphere Insulin; U=units (fill content of TI cartridges or international units for sc RAA).

A standard meal challenge was conducted in patients with T1DM in Trial 117 after 16 weeks of treatment with basal insulin plus either TI or RAA (insulin lispro) (Figure 10). RAA insulin lispro was administered as per label directions, 15 minutes before the meal; TI was administered immediately before the meal. TI administration was associated with a significantly lower baseline-normalized postprandial glucose exposure (AUC_{0-240}).

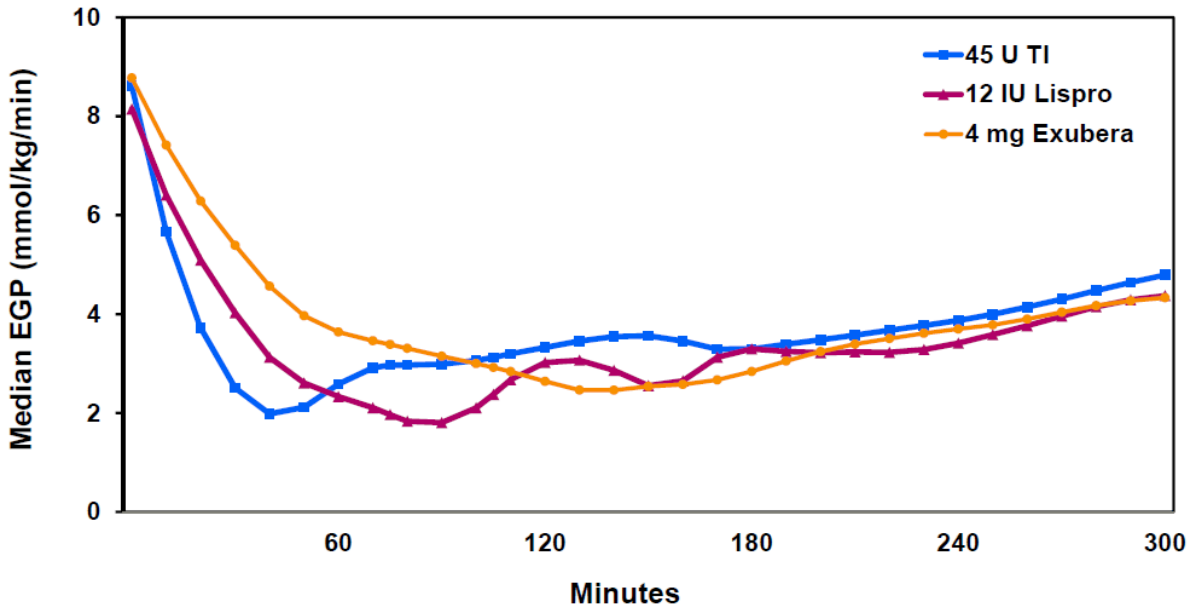
Figure 10: Post-Prandial Glucose at the Week 16 Meal Challenge in Subjects with T1DM (Trial 117)



Abbreviations: TI MedTone N=number of subjects on TI; Humalog N=number of subjects on Humalog (RAA insulin lispro); RAA=rapid-acting analogue (of insulin); TI=Technosphere Insulin.
Note: Time 0=start of the meal.

Part of the glucose-lowering effect of insulin is via suppression of endogenous glucose production (EGP). Figure 11 depicts the time course of EGP suppression following a meal challenge in T2DM subjects (Trial 118) treated either with inhaled TI, inhaled Exubera (a comparator human insulin inhalation powder), or sc RAA insulin lispro. More rapid EGP suppression was noted following TI administration.

Figure 11: Median EGP versus Time after a Meal Challenge in Subjects with T2DM (Trial 118)



Abbreviations: EGP=endogenous glucose production; Exubera=human insulin inhalation powder; IU=international units; lispro=RAA insulin lispro; RAA=rapid-acting analogue (of insulin); T2DM=type 2 diabetes mellitus; TI=Technosphere Insulin; U=units (fill content of TI cartridges).

6.6 FDKP Pharmacodynamics

FDKP alone (ie, no insulin) was studied in a thorough corrected QT (QTc) trial, incorporating a moxifloxicin control, in 48 healthy subjects; safety, electrocardiogram (ECG), and PK data were collected (48 subjects, moxifloxacin; 47 subjects, FDKP) (Trial 131). Time-averaged analysis of the placebo-corrected mean individually-corrected QT (QTcI) change from baseline for supra-therapeutic (40 mg) and therapeutic (20 mg) doses of TI Inhalation Powder without the insulin (0.3 ms and 0.5 ms, respectively) showed no significant effect of FDKP on QTc. Assay sensitivity was reached in that the placebo-corrected mean QTcI change from baseline for moxifloxacin was 5.5 ms (expected, 5 ms to 10 ms). Mean change from baseline for placebo was 3.5 ms, demonstrating that the study was well conducted and that background QTc variability was controlled. Exploratory outlier analysis revealed no QTc imbalances between placebo and supratherapeutic/therapeutic dose groups.

It was concluded by thorough QT/QTc analyses that therapeutic (20 mg) and supratherapeutic (40 mg) doses of TP had no effect on QTc interval as measured by time-matched mean change in QTcI from baseline. As shown by ECG outlier and morphological analyses, therapeutic (20 mg) and supra-therapeutic (40 mg) doses of TP had no effect on heart rate, atrioventricular conduction, or cardiac depolarization as measured in terms of PR and QRS interval durations, and induced no new clinically-relevant morphological changes.

6.7 Converting from Subcutaneous Rapid Acting Analogs to Technosphere Insulin

The TI Inhalation System has been improved over the course of its development. Originally, TI was inhaled using the MedTone inhaler. This device was used in the earlier clinical trials submitted in the 2009 Original NDA. At that time, TI was filled in cartridges for the MedTone inhaler in quantities of 15 U insulin (5 mg TI Inhalation Powder) and 30 U insulin (10 mg TI Inhalation Powder).

The MedTone inhaler was subsequently replaced by the Gen2 inhaler. The TI Inhalation Powder used in the Gen2 inhaler is the same as that used in the MedTone inhaler. However, because the Gen2 inhaler delivers the powder more efficiently than the MedTone inhaler, less powder is needed in each cartridge. For this reason, Gen2 cartridges contain 10 U insulin (3.3 mg TI Inhalation Powder) and 20 U insulin (6.7 mg TI Inhalation Powder).

Analyses of data from recently-completed clinical trials showed a 25% dose ratio between comparator sc insulin and TI. This is consistent with data from recent PK trials showing a bioavailability of 30% for TI compared with sc RHI and sc RAA. Taken as a whole, these data indicate that each TI Gen2 cartridge containing 10 U or 20 U of insulin approximates 3 units or 6 units of sc insulin, respectively.

6.8 Pharmacokinetic and Pharmacodynamic Conclusions

Insulin PK and PD are consistently reproducible after TI administration.

- Absorption from the lungs is rapid with a typical t_{max} of approximately 12 to 15 minutes.
- Insulin exposure (C_{max} and AUC) is dose-proportional from 10 U to 80 U.
- Insulin concentrations return to baseline after approximately 180 minutes.
- This more rapid onset/shorter duration of exposure and action, relative to either RHI or RAA, more closely mimics endogenous prandial insulin secretion/action.
- The 2 inhalers (MedTone and Gen2) provide equivalent exposure after adjusting for the greater efficiency of delivery by the Gen2 inhaler.
- Insulin exposure after TI administration is reduced in subjects with asthma; however, premedication with a bronchodilator eliminates this reduction.
- The insulin PK profiles are unchanged in smokers, subjects with COPD, and subjects with URI. No dose adjustment is necessary for subjects who have a URI and are able to appropriately inhale TI.
- Insulin PK is unchanged when TI is administered with either inhaled steroids or bronchodilators.

FDKP is absorbed rapidly from the lungs, is not metabolized, and is eliminated in the urine. FDKP elimination is reduced in subjects with renal impairment.

7 CLINICAL AND STATISTICAL METHODS

The TI clinical development program was designed to assess the efficacy and safety of TI in subjects with T1DM and those with T2DM, at different stages of the disease, covering the spectrum of patients with diabetes who require insulin treatment.

7.1 Efficacy

7.1.1 Trials Supporting Efficacy

In addition to trials conducted to better understand TI dosing, short-term safety and efficacy, and device utility, 10 Phase 3 efficacy and safety trials were conducted earlier in the course of TI development (Appendix 3); 4 of these had a treatment duration of 16 weeks or longer: 2 trials in subjects with T1DM (Trials 009 and 117) and 2 trials in subjects with T2DM (Trials 102 and 014).

As discussed in Section 3.2, an important limitation to the designs of all the earlier Phase 3 trials included in the 2009 Original NDA and 2010 Amendment was inadequate titration of insulin doses with both TI and comparators. In addition, a new inhaler device, the Gen2 inhaler, was successfully developed (see Section 4). Therefore, to support approvability of TI delivered by the Gen2 inhaler, two new 24-week pivotal efficacy trials were conducted utilizing the to-be-marketed Gen2 device and a treat-to-target, forced titration trial design. These pivotal trials for the 2013 Resubmission, reflecting FDA input, are Trial 171 conducted in T1DM subjects and Trial 175 conducted in T2DM subjects.

Given differences in trial designs and conduct across the entire clinical program, it was agreed with the FDA that the 2013 Resubmission efficacy data would consist of the new pivotal Phase 3 clinical trial results presented as side-by-side comparisons of efficacy with previously conducted Phase 3 clinical trials in T1DM and T2DM. FDA agreed that the new and old trials would not be pooled and reanalyzed for efficacy.

Of the earlier Phase 3 trials, Trial 117 was a 16-week trial that was prematurely terminated for reasons unrelated to trial conduct, efficacy, or safety; Trial 014 was a 24-week trial in which TI prandial titration was limited with a cap on dosing. Both trials were performed with the MedTone inhaler. These 2 trials are not considered pivotal efficacy trials and will not be discussed further; a brief summary of their design and results is provided in Appendix 5. Consequently, four Phase 3 trials constitute the core of TI efficacy data presentation: two in T1DM subjects on a basal/bolus insulin regimen (Trials 171 and 009), and two in T2DM subjects (insulin-naïve failing OAD therapy [Trial 175] or subjects on prior insulin therapy [Trial 102]). As the Gen2 inhaler was used in the 2 more recently-conducted trials, and because their trial design elements were discussed with the FDA, Trials 171 and 175 are considered pivotal for the current submission and are the focus of the data presentation.

7.1.2 General Trial Design Considerations

Table 4 depicts the design features of the four Phase 3 trials. All were randomized, controlled, multi-center, international trials that compared TI with standard-of-care

comparator agents or placebo. Comparator trials (Trials 171, 009, 102) were open-label in design as is the norm for insulin trials and consistent with the 2008 FDA guidance.[40] In these trials, efforts were made to minimize the impact of potential confounding factors. Notably, since TI is administered not as an injection but is orally inhaled, it was feasible to conduct a double-blind placebo-controlled clinical trial (Trial 175) in insulin-naïve T2DM subjects (poorly controlled on OAD therapy) randomized to receive either TI or TP (the placebo powder without insulin) via Gen2 inhalers. This allowed for potential bias minimization, especially with respect to device and over-all tolerability assessment, and helped reduce subjectivity of non-severe hypoglycemia event reporting.

Consistent with insulin trial conduct, the active-control trials had the goal of showing noninferiority with comparator insulin therapy. A noninferiority margin of 0.4 was used, consistent with the margin used in previous Phase 3 trials of FDA-approved prandial insulins (see Section 7.2.2). Comparator choices were made based on typical diabetes treatments. The trials in T1DM (Trials 171 and 009) utilized a standard basal/bolus insulin regimen; each treatment group received basal insulin, and sc RAA insulin aspart was used as the prandial insulin comparator. The trial in T2DM subjects previously treated with insulin (Trial 102) compared TI plus basal insulin to sc premixed biphasic RAA (BPR) 70/30 given twice daily (bid), an insulin comparator commonly used at the time because of the convenience of its twice-daily injections.

Table 4: Design Features in the 2013 Resubmission Efficacy Trials

Design Features	T1DM		T2DM	
	MKC-TI-171	MKC-TI-009	MKC-TI-175	MKC-TI-102
Primary Analysis Population	FAS	mITT[a]	FAS	mITT[a]
Primary Analysis Statistical Measure	Noninferiority	Noninferiority	Superiority	Noninferiority
Pre-enrollment Treatment	Stable basal/bolus × 3 months	Total daily dose insulin ≤ 1.4 IU/kg/day	Stable metformin or 2 or more OADs × 3 months	sc insulin 2 to 3 times daily (w/ or w/o concomitant OADs)
Run-in	4-week basal insulin optimization	None	6 weeks on pre-enrollment OADs	None
Treatment Duration	24 weeks	52 weeks	24 weeks	52 weeks
Treatment Blinding	Open-label	Open-label	Double-blind	Open-label
Randomized Trial Treatment[b]	Pre-trial basal/prandial TI	glargine/prandial TI	Prandial TI/OAD	glargine/prandial TI
Randomized Control Treatment[b]	Pre-trial basal/prandial RAA aspart	glargine/prandial RAA aspart	Prandial TP (placebo)/OAD	BPR 70/30
Titration of TI based on BG measurements	Postprandial	Pre-meal & Postprandial	Postprandial	Pre-meal & Postprandial
Titration period	Weeks 1-12	Entire 52-week trial duration	Weeks 1-12	Entire 52-week trial duration
Inhaler	Gen2 & MedTone	MedTone	Gen2	MedTone
Maximum TI Dose/Meal[1]	4 U/kg/day	90 U/meal	4 U/kg/day	90 U/meal
HbA1c Inclusion Range (at Screening)	≥7.5% and ≤10.0%	>7% and ≤11%	≥7.5% and ≤10.0%	>7% and ≤11%

Abbreviations: FAS=full analysis set; mITT= modified intent-to-treat.
a: In the original CSRs, the term ITT was used instead of mITT, which was the actual population used for efficacy analyses. To provide a precise description of the analyzed population in this document, the term mITT has been used.
b: Basal=basal insulin; prandial=prandial insulin. The basal insulin was either the pre-trial basal, or glargine. The prandial insulin was either TI (or TP) or RAA insulin aspart.

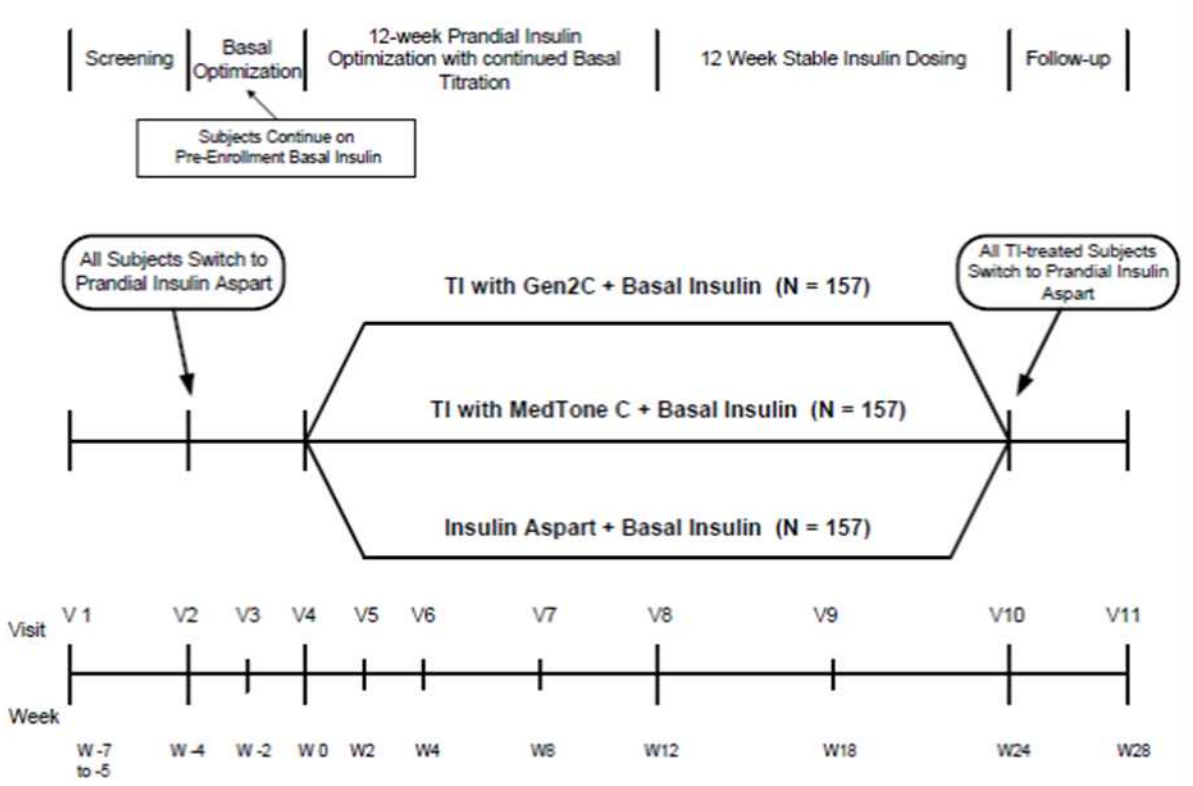
7.1.3 Trial Conduct

7.1.3.1 Type 1 Diabetes Trials

Figure 12 depicts the trial design for Trial 171. Eligible subjects with T1DM who were on a stable basal/bolus insulin regimen entered a 4-week run-in period, during which time all subjects were switched to or maintained on RAA insulin aspart as their prandial insulin. They continued with their pre-trial basal insulin (NPH, glargine, or detemir), which was titrated during this run-in period to achieve FPG between 100 mg/dL (5.6 mmol/L) and 120 mg/dL

(6.7 mmol/L). To be eligible for randomization, subjects had to achieve a FPG ≤180 mg/dL (10.0 mmol/L) during the run-in period. Subjects were trained in the use of electronic diaries to capture self-monitored blood glucose (SMBG) and hypoglycemic events. Eligible subjects randomized to the comparator group continued on their basal insulin/insulin aspart regimen. Eligible subjects randomized to the TI groups (either TI MedTone or TI Gen2) were switched to a new regimen: basal insulin/TI. Insulin dose titration was permitted for the first 12 weeks of the trial; for the subsequent 12 weeks, insulin doses were kept relatively stable and adjusted only for safety reasons or because of a change in a subject's clinical condition (eg, the occurrence of an infection or stress).

Figure 12: Trial Design in Subjects with T1DM (Trial 171)



Abbreviations: N=number of subjects; T1DM=type 1 diabetes mellitus; TI=Technosphere Insulin; V=visit; W=week.

Trial 009 randomized eligible subjects with T1DM to either basal insulin (glargine)/TI or basal insulin (glargine)/insulin aspart in a basal/bolus regimen. The trial did not have a run-in period and titration was permitted over the entire 52-week period.

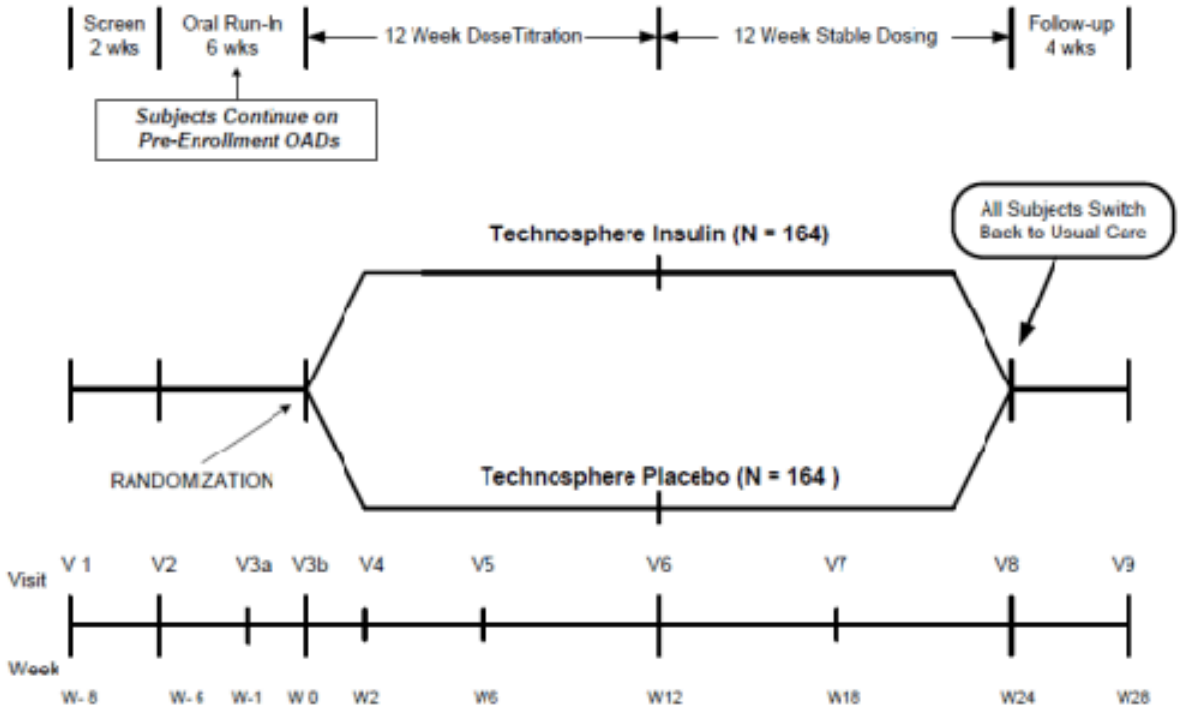
7.1.3.2 Type 2 Diabetes Trials

Figure 13 depicts the trial design for Trial 175. Subjects with T2DM were eligible if they were insulin-naïve with inadequate glycemic control (HbA1c 7.5% to 10.0%) on optimal or maximally-tolerated doses of either metformin monotherapy or ≥2 OADs (ie, they were receiving at least 1.5 g daily or maximum tolerated dose of metformin; at least 50% of the maximum approved dose of sulfonylurea; maximum approved dose for DPP-4 inhibitors; or

maximum tolerated dose of meglitinides or alpha-glucosidase inhibitors). During the 6-week run-in period, subjects continued their pre-study OAD therapy and received nutritional and physical activity counseling and training in the use of glucose meters, SMBG, and electronic diaries. The run-in period was also used to avoid randomization of subjects with improved HbA1c due solely to study procedures (such as routine use of more intensive glucose monitoring and consequent lifestyle/diet changes). Subjects whose HbA1c values had improved to <7.5% after the run-in period were not eligible for randomization.

Following the 6-week run-in period, eligible subjects were randomized to TI or TP (placebo), and underwent a 12-week prandial TI/TP titration phase, with a subsequent 12-week period of stable dosing. During the 24-week treatment phase after randomization, subjects whose hyperglycemia persisted or worsened beyond pre-specified thresholds received open-label rescue therapy in addition to their study treatment. Subjects entering the study on metformin monotherapy were provided glimepiride as rescue therapy when needed. Subjects entering on 2 or more OADs were provided insulin glargine as rescue therapy when needed.

Figure 13: Trial Design in Subjects with T2DM (Trial 175)



Abbreviations: N=number of subjects; OAD=oral anti-diabetic drug; T2DM=type 2 diabetes mellitus; TI=Technosphere Insulin; TP=Techonosphere particles (placebo, no insulin); V=visit; W=week.

Trial 102 randomized eligible subjects who had been receiving sc insulin 2-3 times daily to a basal insulin (glargine)/TI basal/bolus regimen or BPR 70/30 (NovoLog® Mix 70/30 given twice daily [bid]). The trial did not have a run-in period, and titration was permitted over the entire 52-week period.

7.1.4 Insulin Titration Algorithms and TI Conversion Guidelines

Forced titration algorithms that encouraged TI and comparator (or placebo) products to be titrated more appropriately to meet pre-specified treatment goals were utilized in Trials 171 and 175. The treatment algorithms were based on best practice standards, taking into account the distinct PK profiles of RAA insulins and TI. Prandial titration for subjects in the TI and TP groups in Trials 171 and 175 was based on 90-minute post-prandial BG values, whereas subjects in the insulin aspart group (Trial 171) were titrated based on BG values prior to the next meal. Current doses were maintained if the median of the 3 most recent 90-minute post-prandial BG levels was ≥110 mg/dL (6.1 mmol/L) to <160 mg/dL (8.9 mmol/L) in the TI/TP groups or if the median of the 3 most recent pre-prandial BG levels was ≥100 mg/dL (5.6 mmol/L) to <120 mg/dL (6.7 mmol/L) for insulin aspart subjects. Given the shorter duration of action of TI versus RAA insulins, TI-treated subjects were instructed to administer a supplemental dose of TI if the 90-minute postprandial BG level was ≥180 mg/dL (10.0 mmol/L). For subjects in the insulin aspart group, correction doses were allowed by protocol.

In all trials, marketed products were used in a manner consistent with approved labeling. Subjects randomized to receive TI converted from their prandial sc insulin to TI as per pre-specified conversion tables. These conversion tables were intended to conservatively guide the initial switch from RAA to TI. Data obtained during early TI development estimated TI bioavailability at 24% to 28%. For safety considerations, in Trials 009 and 102, a more conservative estimate of the glucose-lowering impact of TI in a MedTone inhaler was assumed, which corresponded to ~ 30% that of sc insulin. This conservative conversion was considered appropriate, given the subjects' unfamiliarity with inhaled insulin titration, to ensure safe use. Therefore, the subjects were instructed that a 15 U TI MedTone cartridge approximated 5 units of sc insulin (ie, to use a 5-unit conversion factor) (Table 5).

Table 5: Conversion from Subcutaneous Insulin to Initial TI Dose with a 5-Unit Conversion Factor (Trials 009 and 102)

RAA (Prandial) Bolus Dose	TI MedTone Dose (Cartridge Fill Content)
0 to 5 IU	15 U
>5 to 10 IU	30 U
>10 to 15 IU	45 U
>15 to 20 IU	60 U
>20 to 25 IU	75 U
>25 to 30 IU	90 U

A subsequent analysis of pooled data from all studies conducted with the MedTone inhaler included in the 2009 submission suggested 25% equivalence to sc insulin (eg, a 15 U TI MedTone cartridge approximated 4 units of sc insulin). Because the insulin delivery using 15 U TI MedTone cartridge was the same as with the 10 U TI Gen2 cartridge, Trial 171 used a 4-unit conversion factor for both the 15 U TI MedTone cartridge and the 10 U TI Gen2 cartridge (Table 6). Subsequent insulin titration was individualized, with TI and aspart doses increased weekly based on the median of three 7-point SMBG determinations each week.

Table 6: Conversion from Subcutaneous Insulin to Initial TI Dose with a 4-Unit Conversion Factor (Trial 171)

RAA (Prandial) Bolus Dose	TI Gen2 Dose (Cartridge Fill Content)	TI MedTone Dose (Cartridge Fill Content)
0 to 4 IU	10 U	15 U
>4 to 8 IU	20 U	30 U
>8 to 12 IU	30 U	45 U
>12 to 16 IU	40 U	60 U
>16 to 20 IU	50 U	75 U
>20 to 24 IU	60 U	90 U

Upon randomization in Trial 175, subjects were started on a 10 U dose of TI or TP per meal. Subjects subsequently self-adjusted their insulin (or placebo) dose on a weekly basis according to a treatment algorithm and the 4-unit conversion factor to guide their TI cartridge incremental dosing.

7.2 Efficacy Endpoints and Statistical Analyses

Efficacy results are presented trial-by-trial (ie, not pooled) as agreed between MKC and the FDA (Section 7.1). Unless otherwise specified, all results presented are based on the original, pre-specified analysis for each trial. Efficacy endpoints and analytical methods are summarized in Table 7.

Note: Unless otherwise specified, mean values presented are observed means.

Table 7: Efficacy Endpoints and Statistical Analyses in the 2013 Resubmission Efficacy Trials

Trial	Inhaler	Trial Treatments for Efficacy Analysis	Primary Endpoint: HbA1c(%) Reduction on Treatment			Secondary Endpoints in the 2013 Resubmission Summary of Efficacy [a]
			Test	Criterion	Analysis Method	
T1DM						
MKC-TI-171[b]	Gen2	TI/basal insulin versus Insulin aspart/basal insulin	Noninferiority after 24 weeks	Upper limit of 95% CI of between group difference <0.4%	MMRM on FAS	HbA1c responder categories FPG 7-point glucose Weight Hypoglycemia
MKC-TI-009[c]	MedTone	TI/basal insulin versus Insulin aspart/basal insulin	Noninferiority after 52 weeks	Upper limit of 95% CI of between group difference <0.4%	ANCOVA with LOCF on mITT	HbA1c responder categories FPG PPG 7-point glucose Weight Hypoglycemia
T2DM						
MKC-TI-175	Gen2	TI + OAD versus TP + OAD	Superiority after 24 weeks	Larger HbA1c reduction in the TI group ($p < 0.05$)	MMRM on FAS (1-sided test at the 0.025 alpha level)	HbA1c responder categories FPG 7-point glucose Weight Hypoglycemia
MKC-TI-102	MedTone	TI/basal insulin versus BPR 70/30 (premixed insulin)	Noninferiority after 52 weeks	Upper limit of 95% CI of between group difference <0.4%	ANCOVA with LOCF on mITT	HbA1c responder categories FPG PPG 7-point glucose Weight Hypoglycemia

Abbreviations: ANCOVA=analysis of covariance; CI=confidence interval; LOCF=last observation carried forward; MMRM=mixed model repeated measures.
a: These secondary endpoints were selected for the integrated summary of efficacy and may differ from those specified in the individual CSRs. P-values for these secondary endpoints are provided elsewhere in this document for descriptive purposes only because the approach for controlling type 1 error within the individual studies was either not fully pre-specified or because an earlier stage in a step-down procedure was not passed.
b: MKC-TI-171 also included a third treatment group (TI MedTone) for analyses of safety outcomes only.
c: Mixed Model Repeated Measures analysis was also performed to provide more uniform comparison among T1DM trials.

7.2.1 Analyses Sets

Efficacy analyses were done with several analysis sets defined below:

- The full analysis set (FAS) consisted of all randomized subjects. All efficacy analyses were performed based on the randomized treatment assignment regardless of the actual treatment the subject received during the trial.
- The modified intent-to-treat (mITT) population (termed the intent-to-treat [ITT] population in the old clinical trial reports) included all randomized subjects who received at least one dose of trial drug and had a baseline and at least 1 post-baseline value for HbA1c (%). All analyses were performed based on the treatment to which a subject was randomized regardless of the actual treatment the subject received.
- The per protocol (PP) population consisted of all randomized subjects who completed the randomized treatment period and who were deemed to be protocol compliant. To be considered protocol compliant, a subject could not have had any major protocol violations during the study. Major protocol violations were identified in a blinded manner prior to database lock.

7.2.2 Primary Endpoint: HbA1c Reduction during the Treatment Period

In the 3 noninferiority trials against active comparators (Trials 171, 009, and 102), the pre-specified noninferiority margin was 0.4% and the upper limit of the 95% CI for the between treatment group difference is required to be less than this value. This margin represents the maximum degree of inferiority of the test drug relative to the control drug that the trial must exclude statistically. This noninferiority margin has been routinely used in Phase 3 noninferiority diabetes trials that compare 2 different prandial insulin therapies, and was selected with guidance provided by the FDA.

In 52-week Trials 009 and 102, primary efficacy analyses (analysis of covariance [ANCOVA]) were performed based on the mITT population.

To better handle missing data and per agreement with the FDA, HbA1c was analyzed using Mixed Model Repeated Measures (MMRM) in Trials 171 and 175 with HbA1c measurement as the dependent variable and explanatory variables of region, basal insulin (Trial 171) or OAD type (Trial 175), visit (categorical time in weeks), treatment, visit by treatment as fixed effects and subject as random effect. To account for all the collected data and all randomized subjects, including subjects for whom only baseline or post-baseline measurements were available, HbA1c instead of HbA1c change from baseline was used as the dependent variable. In addition, change from baseline was calculated using adjusted baseline and post-baseline HbA1c from the MMRM model. Covariance structures of autoregression (1) [AR(1)], unstructured [UN] and Toeplitz [TOEP] were evaluated and AR(1) was applied for the primary analysis. This analysis was performed based on the FAS which included all randomized subjects. For subjects who prematurely discontinued trial treatment or received rescue medication, the post-baseline HbA1c data up to the time of discontinuation of trial treatment or use of rescue medication was included in the analysis. For subjects who completed the randomized treatment, all data from the 24-week treatment period was included in the analysis. The 2-sided 95% CIs for change from baseline at Week 24 were

constructed from the least squares means for the treatment difference (TI Gen2 vs. insulin aspart in Trial 171; TI Gen2 vs Placebo in Trial 175) at Week 24 and then subtracting the corresponding least squares means for treatment difference at Week 0.

Sensitivity analyses were conducted for the primary endpoint in several of the trials. Both Trials 171 and 175 included sensitivity analyses to examine the effect of subjects who discontinued trial treatment prematurely. A Pattern Mixture model was performed to explore the impact of missing data on treatment difference, with explanatory variables of baseline HbA1c, region, basal therapy (insulin in Trial 171 and OADs in Trial 175) stratum, treatment group, visit (categorical time in weeks), discontinuation pattern (time of discontinuation), treatment × visit, treatment × pattern, visit × pattern, treatment × visit × pattern as fixed effect and subject as random effect and HbA1c measurement as the dependent variable. Due to the small number of subjects who discontinued at each visit, subjects were divided into groups depending on their missing data to form the patterns. Interactions among treatment, visit and discontinuation pattern were examined to evaluate the impact of discontinuation pattern on the estimate of HbA1c change from baseline. In addition, for Trial 175, data collected after rescue therapy were also included in a sensitivity analysis.

7.2.3 Secondary Efficacy Endpoints and Analyses

Proportions of HbA1c responder thresholds, fasting plasma glucose, 7-point glucose profiles, change from baseline in weight and hypoglycemia were evaluated in all trials. Longitudinal data were generally analyzed by employing MMRM or ANCOVA analysis. Categorical data were analyzed using logistic regression analysis.

In Trials 171 and 175, all hypoglycemia measures were considered to be safety endpoints. In Trials 102 and 009, one hypoglycemia measure was considered under secondary efficacy, but all other measures of hypoglycemia were considered to be safety endpoints. However, given that hypoglycemia occurs within the context of increasing insulin titration to achieve glycemic control, the hypoglycemia data will be discussed in the efficacy section of this Briefing Document (Section 8.3). Although different definitions of hypoglycemia were used in the later and earlier trials (Table 8), all hypoglycemic episodes characterized by the presence of life-threatening neuroglycopenic symptoms and requirement for assistance from another person were captured across all trials in the severe hypoglycemia category. Also, hypoglycemia was consistently reported as a serious adverse event (SAE) if the hypoglycemia was associated with coma or loss of consciousness, was a hypoglycemic seizure, or met other standard SAE criteria.

Hypoglycemia event rate was analyzed by using the general estimating equation (GEE) (Trials 009 and 102) or negative binomial analysis (Trials 171 and 175) to account for subject effect and different exposure time.

Table 8: Definitions of Hypoglycemia in the Pivotal T1DM and T2DM Trials

	Mild/Moderate Hypoglycemia	Severe Hypoglycemia
T1DM		
MKC-TI-171	• SMBG levels < 70 mg/dL (3.9 mmol/L) and/or • Symptoms of hypoglycemia that were relieved by the self-administration of carbohydrates	• Any event of hypoglycemia that required assistance of another person (not merely requested) who actively administered carbohydrate, glucagon, or other resuscitative actions
MKC-TI-009	• Hypoglycemia-like symptoms (eg, lightheadedness, palpitations, sweats, tremulousness, and headache) and a BG measurement ≤ 63 mg/dL (3.5 mmol/L); or • In the absence of a BG measurement, hypoglycemia-like symptoms that were relieved with carbohydrate intake or self-administered glucagon injections; or • A BG measurement ≤ 49 mg/dL (2.7 mmol/L) and > 36 mg/dL (2.0 mmol/L)	Blood glucose was ≤ 36 mg/dL (2.0 mmol/L), or when the subject experienced the 3 parameters listed below: • The subject required the assistance of another person, and • The subject exhibited at least 1 cognitive neurologic symptom (memory loss, confusion, uncontrollable behavior, irrational behavior, unusual difficulty in awakening, seizure, loss of consciousness), and • Measured BG was ≤ 49 mg/dL (2.7 mmol/L) or, in the absence of a BG measurement, clinical symptoms were reversed by oral carbohydrates, sc glucagon, or intravenous glucose administration
T2DM		
MKC-TI-175	• SMBG levels < 70 mg/dL (3.9 mmol/L) and/or • Symptoms of hypoglycemia that were relieved by the self-administration of carbohydrates	• Any event of hypoglycemia requiring assistance of another person (not merely requested) to actively administer carbohydrate or glucagon
MKC-TI-102	• Hypoglycemia-like symptoms (eg, lightheadedness, palpitations, sweats, tremulousness, and headache) and a BG measurement of≤ 63 mg/dL (3.5 mmol/L); or • In the absence of a BG measurement, hypoglycemia-like symptoms that were relieved with carbohydrate intake or self-administered glucagon injections; or • Any BG measurement ≤ 49 mg/dL (2.7 mmol/L) and > 36 mg/dL (2.0 mmol/L)	Any measured BG was ≤ 36 mg/dL (2.0 mmol/L), or when the subject experienced the 3 parameters listed below: • The subject required the assistance of another person, and • The subject exhibited at least 1 cognitive neurological symptom (memory loss, confusion, uncontrollable behavior, irrational behavior, unusual difficulty in awakening, seizure, loss of consciousness), and • Measured BG was ≤ 49 mg/dL (2.7 mmol/L), or, in the absence of a BG measurement, clinical symptoms were reversed by oral carbohydrates, sc glucagon, or intravenous glucose administration

Abbreviations: BG=blood glucose; sc=subcutaneous; SMBG=self-monitoring of blood-glucose; T1DM=type 1 diabetes mellitus; T2DM=type 2 diabetes mellitus.

Additionally, patient-reported outcomes (PRO) analyses were performed in various studies. The ITQ was used to assess usability and human factors for the Gen2 inhaler. Health state score (visual analog scale) from the EuroQol 5D assessment of health outcomes instrument (EQ-5D) and a Fear of Hypoglycemia Survey were also evaluated.

7.3 Safety

7.3.1 Clinical Trials Supporting Long-Term Safety

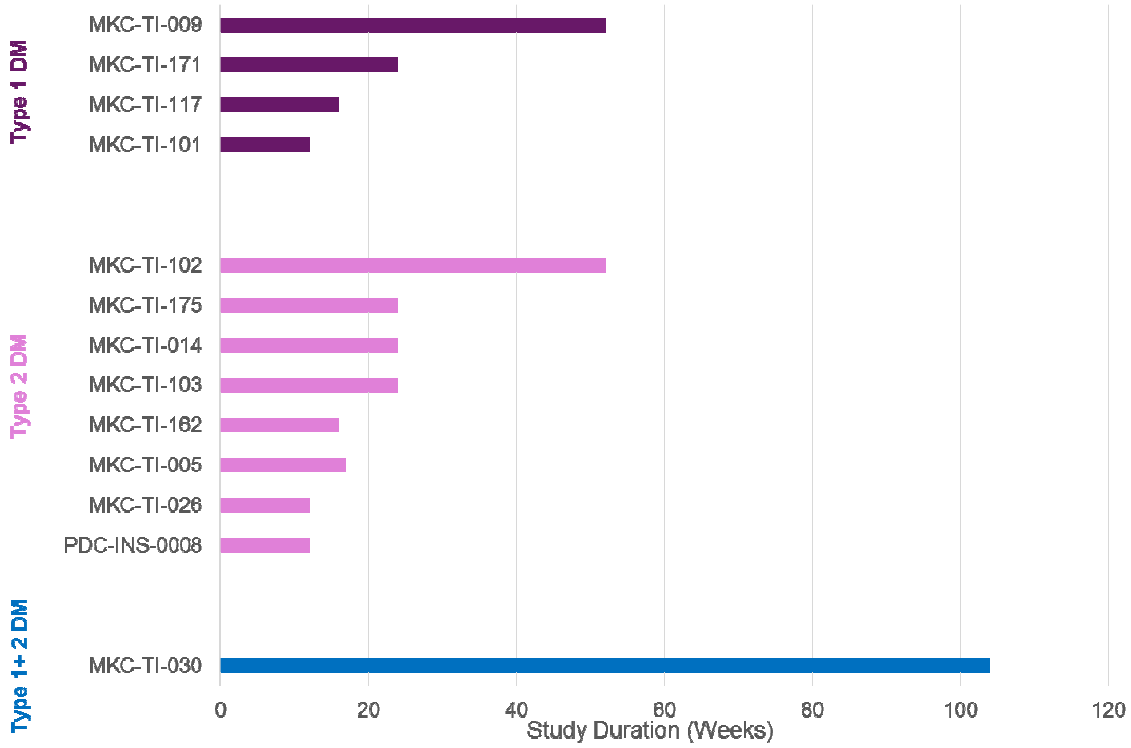
Appendix 3 provides a tabular summary of clinical trials supporting long-term safety of TI. Safety data from all controlled Phase 2/3 clinical trials completed as of 31 Jul 2013 with a planned continuous study treatment exposure >14 days constitute the pooled 2013 Resubmission Safety Population data (Table 9 and Figure 14). Trial 030 was conducted in 1889 T1DM and T2DM subjects to provide long-term pulmonary safety data. It was 104 weeks in treatment duration and compared TI with usual care. The trial also enrolled 164 subjects without diabetes to provide comparable longitudinal pulmonary safety data.

Table 9: 2013 Resubmission Safety Population: Controlled Phase 2/3 Trials > 14 Days of Planned Continuous Exposure to Treatment

Type of Diabetes Mellitus	Trials
T1DM	MKC-TI-009, MKC-TI-030, MKC-TI-101, MKC-TI-117, MKC-TI-171
T2DM	MKC-TI-005, MKC-TI-014, MKC-TI-026, MKC-TI-030, MKC-TI-102, MKC-TI-103, PDC-INS-0008, MKC-TI-175, MKC-TI-162

Note: For MKC-TI-014, only the first 6-month treatment period data are included in the pooled analyses. During the remaining period subjects were off trial treatment.

Figure 14: Treatment Duration in the Pooled Trials in the 2013 Resubmission Safety Population



Abbreviation: DM=diabetes mellitus.

Additional long-term safety data, primarily for pulmonary function and anti-insulin antibody (IAB) development, were obtained from Trial 010, an uncontrolled extension trial for up to 48 additional months of follow-up in 229 subjects with T2DM who had previously completed Trial PDC-INS-0008 or Trial 005. The 24-week Trial 014 in T2DM included a 22-week post-treatment follow-up period for additional pulmonary function assessments; during this period, subjects took conventional therapy. Lastly, subjects who completed participation in 1 of 4 trials (Trials 009, 102, 103, or 030) were eligible to participate in a pulmonary safety follow-up trial (Trial 126). After completion of the parent trial, all subjects who had been randomized to TI returned to their usual anti-diabetic regimen and pulmonary function tests (PFTs) were done at 1 month and 3 months after the end of treatment (EOT) in the parent trial. A tabular summary of these trials is presented in Appendix 3.

7.3.2 Safety Population, Endpoints, and Statistical Analyses

The 2013 Resubmission includes all safety data from all clinical studies regardless of device. Most safety data are presented for the 2013 Resubmission Safety Population. Deaths are presented for the entire TI clinical program including trials not included in the 2013 Resubmission Safety Population. Pulmonary safety is presented as respiratory TEAEs for the 2013 Resubmission Safety Population, PFTs by a specific pooling strategy described in Section 9.5.1, and pulmonary safety in subjects with asthma or COPD by individual trials. Safety data from completed Phase 1 and Phase 2 clinical pharmacology studies with

≤14 days of treatment exposure are presented as a brief general summary of safety. Safety data from ongoing Phase 3 Trials 134 and 139 (trial descriptions and data in Section 9.11.2) are presented as data from individual trials. The safety population was defined as all subjects who took at least one dose of trial drug, including basal insulin. Subjects were analyzed for safety based on the actual treatment they received.

8 CLINICAL EFFICACY

Data supporting TI efficacy are presented for the pivotal Phase 3 T1DM Trials 171 and 009 and T2DM Trials 175 and 102. Consistent results have been seen across all trials in efficacy parameters of glycemic control, weight, and hypoglycemia.

- In clinical trials, across a broad spectrum of diabetes severity, TI was noninferior to active comparators in 2 of 3 trials (Trials 171 in T1DM and 102 in T2DM, but not 009 in T1DM) and superior to placebo (Trial 175 in T2DM) in HbA1c reduction as demonstrated in 24 to 52-week clinical trials. The glycemic lowering effect was durable, as noted in the trials with 52-week treatment duration.
- A greater percentage of T2DM subjects attained target HbA1c goals with TI than with placebo; and, as expected in noninferiority trials, TI and insulin comparators, on the whole, were similar in their target achievements, although more subjects treated with RAA insulin aspart than with TI achieved HbA1c ≤ 7.0% in Trial 171.
- In the active comparator trials, a greater reduction in FPG was noted with a TI plus basal insulin regimen versus an insulin comparator regimen (RAA insulin aspart plus basal insulin in Trials 171 and 009; BPR 70/30 bid in Trial 102).
- Clinically relevant between-treatment differences favoring TI versus insulin comparators were noted for end-treatment weight change, as TI-treated subjects either lost weight (T1DM) or had less weight gain (T2DM) than that seen in comparator insulin-treated subjects. In insulin-naïve T2DM subjects on OADs, the weight advantage favored the placebo group (Trial 175).
- Seven-point glucose profiles demonstrated less prandial glycemic excursion.
- In all 3 trials in insulin-using diabetics, both T1DM and T2DM, TI was associated with a clinically meaningful reduction in severe hypoglycemia event rates from that of comparators (20% [Trial 009], 43% [Trial 171] and 65% [Trial 102] reductions). Overall, in the active comparator trials, clinically relevant decreases were noted in:
  - the incidence of severe hypoglycemia and all-severity hypoglycemic event rate (T1DM; Trial 171)
  - The incidence of all-severity hypoglycemia (T1DM; Trial 009)
  - The incidence of all-severity and severe hypoglycemia, and all-severity hypoglycemic event rate (T2DM; Trial 102)
- Compared to TP (placebo), TI was associated with a greater incidence of any hypoglycemia and a small increase in severe hypoglycemic event rates (T2DM; Trial 175). When analyzed by background OAD use, the event rate of all hypoglycemic events in TI subjects on metformin was not different than the event rate in placebo subjects on metformin and SU, a very commonly used therapeutic 2-drug combination therapy.

The efficacy section is organized as follows:

- Disposition, Demography, and Baseline Characteristics
- Glycemic Efficacy, Weight, and Insulin Doses in T1DM:
  - HbA1c reduction during treatment
  - HbA1c goal attainment
  - FPG changes
  - Weight changes
  - 7-point glucose profiles
  - TI and basal insulin doses
- Glycemic Efficacy, Weight, and Insulin Doses in T2DM:
  - Same subtopics as for T1DM
- Hypoglycemia for both T1DM and T2DM
- Patient Reported Outcomes (PRO) results
- TI dosing recommendations and conversion between TI and sc insulin

Although Trial 171 used both inhalers, this section includes data only for the TI Gen2 group because the purpose for the MedTone treatment group, as specified by protocol, was for a safety comparison of the devices (Section 9.5).

8.1 Baseline Characteristics and Disposition

No notable differences were seen in age, race, BMI, and baseline HbA1c between TI and comparator groups, for both the T1DM and T2DM populations (Table 10). Compared with the respective TI groups, the comparator group in Trial 171 weighed less and had a longer median duration of DM, and the comparator group in Trial 009 had a lower median FPG at baseline. Comparing across diabetes types, the T1DM subjects were younger, weighed less, and had longer histories of diabetes than the T2DM subjects.

In the trials, subjects in the United States represented approximately 40% (Trial 171) to 50% (all others) of the study population.

Table 10: Baseline Characteristics of Subjects in T1DM and T2DM Trials (Efficacy Populations)

Parameter	T1DM				T2DM			
	MKC-TI-171		MKC-TI-009		MKC-TI-175		MKC-TI-102	
	TI Gen2 (N=174)	Comparator[a] (N=170)	TI (N=277)	Comparator[a] (N=262)	TI Gen2 (N=177)	TP (N=176)	TI (N=302)	Comparator[a] (N=316)
Age								
Mean±SD	37.0±12.42	39.1±12.63	37.9±13.09	38.2±13.27	56.7±9.10	56.7±8.51	55.9±10.61	55.9±9.98
Median	36.0	36.5	36.0	37.0	57.0	57.0	56.0	56.0
Range	(18, 71)	(18, 76)	(18, 69)	(18, 76)	(27, 75)	(36, 79)	(19, 79)	(24, 78)
Ethnicity/Race, n(%)								
Caucasian	164 (94.3)	166 (97.6)	237 (85.6)	227 (86.6)	151 (85.3)	155 (88.1)	202 (66.9)	215 (68.0)
Black	8 (4.6)	3 (1.8)	18 (6.5)	14 (5.3)	21 (11.9)	17 (9.7)	25 (8.3)	27 (8.5)
Hispanic	17 (9.8)	18 (10.6)	13 (4.7)	17 (6.5)	43[e] (24.3)	41[e] (23.3)	61 (20.2)	64 (20.3)
Asian	1 (0.6)	0	5 (1.8)	1 (0.4)	1 (0.6)	2 (1.1)	8 (2.6)	4 (1.3)
Pacific Islander	1 (0.6)	0	NA	NA	NA	NA	NA	NA
Native American	0	0	NA	NA	1 (0.6)	1 (0.6)	NA	NA
Other	0	1 (0.6)	4 (1.4)	3 (1.1)	3 (1.7)	1 (0.6)	6 (2.0)	6 (1.9)
Sex, n(%)								
Male	77 (44.3)	74 (43.5)	146 (52.7)	136 (51.9)	82 (46.3)	74 (42.0)	153 (50.7)	137 (43.4)
Female	97 (55.7)	96 (56.5)	131 (47.3)	126 (48.1)	95 (53.7)	102 (58.0)	149 (49.3)	179 (56.6)
Weight (kg)								
Mean±SD	75.7±15.75	72.6±15.28	76.6±15.61	76.8±14.95	90.2±17.22	90.8±17.34	88.3±17.39	85.8±17.96
Median	74.4	69.9	75.0	75.0	88.4	88.6	86.8	85.1
Range	(41.7, 129.4)	(46.6, 120.2)	(45.6, 131.9)	(42.2, 123.1)	(54.0, 142.3)	(58.0, 136.6)	(48.3, 140.8)	(47.4, 135.8)

Table 10: Baseline Characteristics of Subjects in T1DM and T2DM Trials (Efficacy Populations)

Parameter	T1DM				T2DM			
	MKC-TI-171		MKC-TI-009		MKC-TI-175		MKC-TI-102	
	TI Gen2 (N=174)	Comparator[a] (N=170)	TI (N=277)	Comparator[a] (N=262)	TI Gen2 (N=177)	TP (N=176)	TI (N=302)	Comparator[a] (N=316)
BMI (kg/m^2)								
Mean±SD	26.0±4.48	25.4±4.11	26.1±3.96	26.2±3.64	31.8±4.92	32.4±5.00	31.6±4.85	31.1±4.91
Median	25.7	24.5	25.6	25.8	31.3	31.6	31.6	31.1
Range	(16.6, 38.6)	(17.4, 37.2)	(17.3, 38.1)	(17.8, 36.0)	(21.6, 44.6)	(21.1, 44.4)	(19.6, 44.2)	(19.4, 40.9)
Duration of DM (y)								
Mean±SD	16.0±10.27	16.7±10.04	18.1±11.46	18.7±11.63	9.7±5.79	9.2±5.38	13.0±7.18	13.7±7.88
Median	13.8	16.0	16.2	15.5	9.0	8.3	11.5	12.3
Range	(1.1, 57.3)	(1.0, 42.2)	(1 ,61)	(1, 64)	(1.1, 34.7)	(1.0, 28.8)	(0, 34)	(0, 52)
Baseline HbA1c (%)								
Mean±SD	8.0±0.77	7.9±0.75	8.4±0.92	8.5±0.97	8.3±0.68	8.4±0.78	8.7±1.12	8.7±1.08
Median	7.9	7.9	8.3	8.4	8.10	8.30	8.6	8.6
Range	(6.2, 10.6)	(5.8, 10.1)	(6.6, 11.6)	(5.7, 12.0)	(6.6, 10.1)	(5.1, 10.9)	(6.6, 11.5)	(6.6, 12.7)
Baseline FPG (mg/dL)								
Mean±SD	155.0±67.62	151.2±67.43	187.6±85.13	180.8±85.87	179.1±43.72	177.2±46.40	169.3±65.78	176.7±67.35
Median	144.5	148.0	181.0	169.6	172.0	171.5	163.0	165.5
Range	(21.0, 403.0)	(23.0, 375.0)	(24.0, 445.1)	(29.0, 465.0)	(49.0, 306.0)	(54.0, 316.0)	(1.0, 404.0)	(2.0, 413.0)

Abbreviations: FAS=full analysis set; FPG=fasting plasma glucose; mITT=modified intent-to-treat; NA=not applicable or not available in the original clinical trial report; PP=per protocol; TI=Technosphere Insulin; TP=Technosphere particles (placebo, no insulin).

a: Comparators in T1DM trials were sc RAA; Comparator in Trial MKC-TI-102 was premixed insulin (BPR 70/30).

Note: Not all subjects had data for all categories of demographic and baseline characteristics; thus, the number of subjects for each category may not be exactly the number of subjects in the column header.

Table 11 depicts the disposition of subjects in the 4 clinical trials after Sponsor review of each case to identify hyperglycemia/lack of efficacy and to further investigate the reasons for discontinuation in cases initially noted as withdrawals of consent, investigator decision, and other.

In the active-controlled trials, more subjects in the TI-treated group than the comparator group discontinued trial participation prematurely, with a greater percentage of subjects discontinuing in the 52-week trials (Trials 102 and 009). In the placebo-controlled trial, a greater proportion of TP-treated subjects discontinued prematurely compared to subjects in the TI group (Trial 175).

Overall, the most common reason for premature trial discontinuation was due to withdrawal of consent. The majority of these reasons were related to personal issues such as work/family conflicts, relocation, and no longer wanting to participate in the study. In the active-controlled trials, more TI-treated subjects than comparator-treated subjects discontinued because of adverse events not related to hyperglycemia; for these TI-treated subjects, the most common TEAE leading to discontinuation was cough. In Trial 009, more TI-treated subjects discontinued because of hyperglycemia or lack of efficacy.

Lack of experience with a new insulin product may have influenced TI continuation rate; patients treated with comparator insulin products were receiving the standard-of-care treatment with which they were quite familiar, and upon discontinuation would have fewer treatment options. In addition, subjects discontinuing TI treatment always had the option to go back to using their pre-trial RAA or RHI prandial insulin. Open-label design may have influenced these results as well: a lower discontinuation rate was noted for TI in the double-blind, placebo-controlled Trial 175 versus that seen with TI in the other trials, and the rate was lower than for placebo.

Table 11: Disposition of Subjects in the Four Key Phase 3 Efficacy Trials

Population	T1DM				T2DM			
	MKC-TI-171		MKC-TI-009		MKC-TI-175		MKC-TI-102	
	TI Gen2 n (%)	Comparator[a] n (%)	TI n (%)	Comparator[a] n (%)	TI Gen2 n (%)	TP n (%)	TI n (%)	Comparator[a] n (%)
Percentages based on the randomized population								
Screened	1401		1420		1379		2064	
Randomized	174 (100)	170 (100)	301 (100)	288 (100)	177 (100)	176 (100)	334 (100)	343 (100)
FAS	174 (100)	170 (100)	301 (100)	288 (100)	177 (100)	176 (100)	NA	NA
mITT	NA	NA	277 (92.0)	262 (91.0)	NA	NA	302 (90.4)	316 (92.1)
Safety	174 (100)	171[b] (100)	293[c] (97.3)	272 (94.4)	177 (100)	176 (100)	323 (96.7)	331 (96.5)
Completed	130 (74.7)	151 (88.8)	198[c] (65.8)	220 (76.4)	150 (84.7)	139 (79.0)	216 (64.7)	246 (71.7)
Discontinued	44 (25.3)	19 (11.2)	94[c] (31.2)	52 (18.1)	27 (15.3)	37 (21.0)	107 (32.0)	85 (24.5)
Hyperglycemia & lack of efficacy	5 (2.9)	0 (0.0)	23 (7.6)	2 (0.7)	1 (0.6)	4 (2.3)	14 (4.2)	10 (2.9)
Other AEs (not related to hyperglycemia)	16 (9.2)	0 (0.0)	20 (6.6)	4 (1.4)	7 (4.0)	9 (5.1)	32 (9.6)	10 (2.9)
Protocol Violation	5 (2.9)	2 (1.2)	3 (1.0)	14 (4.9)	4 (2.3)	9 (5.1)	6 (1.8)	3 (0.9)
Subject Withdrew Consent	17 (9.8)	8 (4.7)	29 (9.6)	15 (5.2)	8 (4.5)	11 (6.3)	37 (11.1)	28 (8.2)
Subject Died	0 (0.0)	1 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	4 (1.2)	1 (0.3)
Investigator Decision	0 (0.0)	0 (0.0)	7 (2.3)	7 (2.4)	1 (0.6)	0 (0.0)	3 (0.9)	4 (1.2)
Pregnancy	0 (0.0)	4 (2.4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Lost to Follow-Up	1 (0.6)	4 (2.4)	5 (1.7)	5 (1.7)	6 (3.4)	4 (2.3)	6 (1.8)	21 (6.1)
Other	0 (0.0)	0 (0.0)	7 (2.3)	5 (1.7)	0 (0.0)	0 (0.0)	5 (1.5)	6 (1.7)

a: Comparators in T1DM trials were sc RAA; Comparator in Trial MKC-TI-102 was premixed insulin (BPR 70/30).

b: In Trial 171, one subject randomized to TI MedTone was mistakenly given comparator treatment instead.

c: In Trial 009, in the TI group, one subject was not documented as either completing the study or discontinuing the study.

Note: This table reflects numbers after Sponsor review of each case to identify hyperglycemia/lack of efficacy and further investigate cases initially noted (based on verbatim terms provided by the Investigator) as withdrawals of consent, Investigator decision, and other.

8.2 Glycemic Efficacy, Weight Changes, and Insulin Dosing

8.2.1 Type 1 Diabetes Mellitus (Trials 171 and 009)

8.2.1.1 HbA1c Change from Baseline (Primary Efficacy Endpoint)

Results for HbA1c change from baseline to the end of treatment for Trials 171 and 009 are presented in Table 12 and Figure 15.

In Trial 171, the adjusted mean baseline HbA1c levels were comparable between treatment groups (7.94%, TI group; 7.92% insulin aspart group), and decreased to mean HbA1c levels of 7.73% and 7.52%, respectively, at Week 24, with a between-group difference 0.19% with 95% CI [0.02, 0.36]. Based on pre-specified noninferiority criteria (Table 7), Trial 171 met its primary endpoint; TI plus basal insulin was noninferior to insulin aspart plus basal insulin in mean HbA1c change from baseline at Week 24.

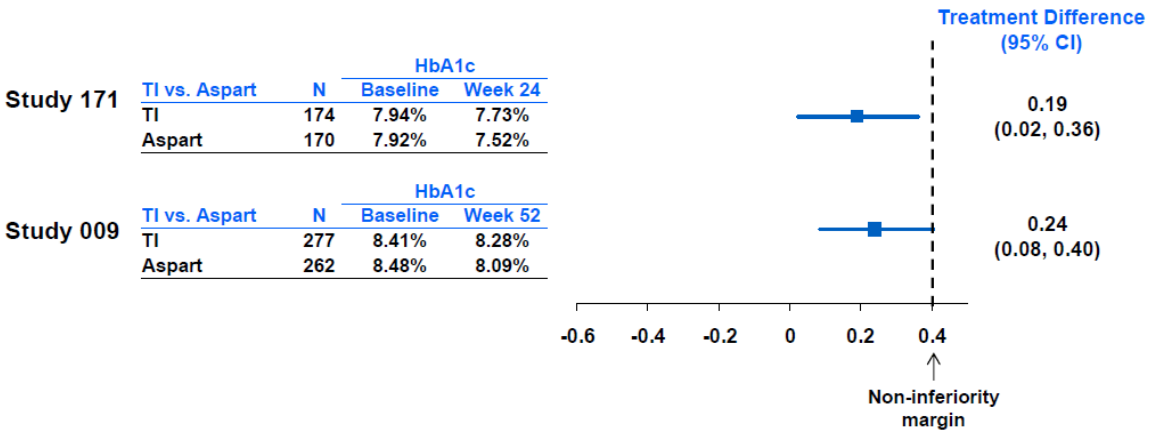
In Trial 009, the adjusted mean baseline HbA1c levels were higher than in Trial 171 but were similar between treatment groups (8.41%, TI group; 8.48%, insulin aspart group). They decreased to mean HbA1c levels of 8.28% and 8.09%, respectively, at Week 52. The between-group treatment difference was 0.24%, favoring insulin aspart; the upper limit of the 95% CI for the between-group difference was at the 0.4% noninferiority margin (not < 0.4% as pre-specified), thus Trial 009 did not meet its primary efficacy endpoint of noninferiority of TI compared with insulin aspart after 52 weeks of treatment.

Table 12: HbA1c (%) Change from Baseline in T1DM Trials

Statistic	TI	Comparator	Treatment Difference TI – Comparator
Trial MKC-TI-171[a] Week 24			
Number of Subjects	174	170	
Baseline HbA1c (%)	7.94	7.92	
Adjusted Mean Change (SE), %	-0.21 (0.062)	-0.40 (0.060)	0.19 (0.086)
95% CI	(-0.33, -0.09)	(-0.52, -0.28)	(0.02, 0.36)
Trial MKC-TI-009[b] Week 52			
Number of Subjects	277	262	
Baseline HbA1c (%)	8.41	8.48	
Adjusted Mean Change (SE), %	–0.13 (0.058)	–0.37 (0.059)	0.24 (0.082)
95% CI	(–0.24, –0.01)	(–0.49, -0.25)	(0.08, 0.40)

a: For Trial MKC-TI-171 (only TI Gen2 group shown), TI inhaler: Gen2; comparator: insulin aspart; analysis population: FAS; primary analysis of change from baseline at Week 24 in HbA1c (%): MMRM
b: For Trial MKC-TI-009, TI inhaler: MedTone; comparator: insulin aspart; analysis population: mITT Population with LOCF; primary analysis of change from baseline at Week 52 in HbA1c (%): ANCOVA

Figure 15: Between Group Differences in HbA1c (%) Change from Baseline to End of Treatment in T1DM Trials



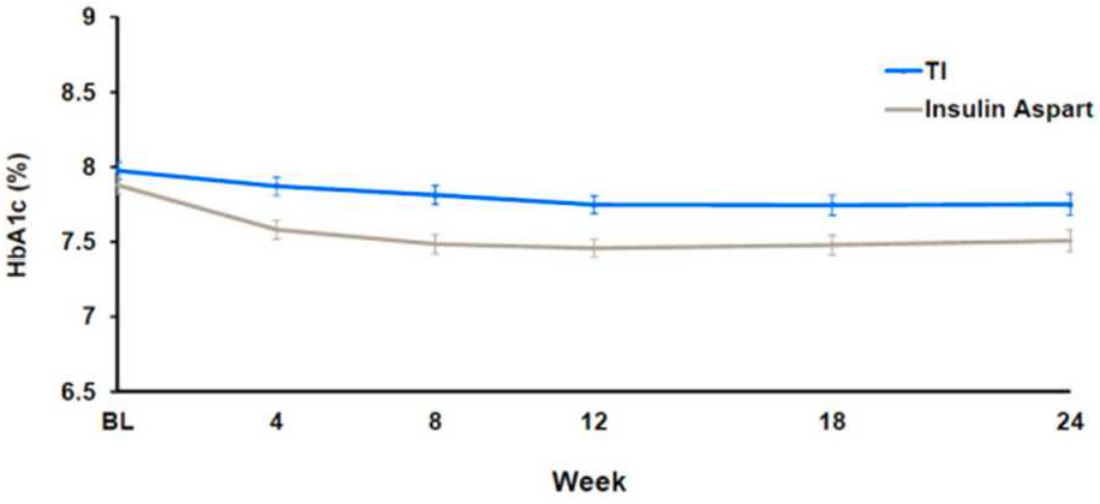
Note: Graph shows point estimate and 95% CI of the between group difference (TI minus comparator). Baseline is model-adjusted.

Figure 16 and Figure 17 depict the mean HbA1c change over time achieved in the Trials 171 and 009.

In Trial 171, the observed (unadjusted) mean HbA1c values at Screening were 8.50% and 8.56% for TI and insulin aspart groups, respectively. HbA1c values declined substantially (-0.52% TI, -0.68% insulin aspart) during the pre-randomization run-in period, as subjects converted to prandial insulin aspart and titrated their pre-trial basal insulin twice a week for 4-weeks. Following randomization, insulin aspart group continued on the same treatment regimen, with HbA1c levels starting to plateau at Week 8 (Figure 16). In contrast, for the TI group, the switch from insulin aspart to TI, which required a new titration algorithm and becoming familiar with a new device, resulted in a slower decline in HbA1c over the next 8 weeks (mean change from baseline: -0.14, TI; -0.42, insulin aspart). Both groups stopped further dose titration by Week 12, as required by protocol, and maintained a stable HbA1c for the duration of the trial, with a mean decline in HbA1c from baseline to Week 24 of -0.21% and -0.40% for TI and insulin aspart, respectively.

In Trial 009 (Figure 17) both TI and insulin aspart groups achieved a durable glycemic effect over a 52-week period with a maximal/near-maximal effect achieved by Week 14 that was sustained through the end of treatment.

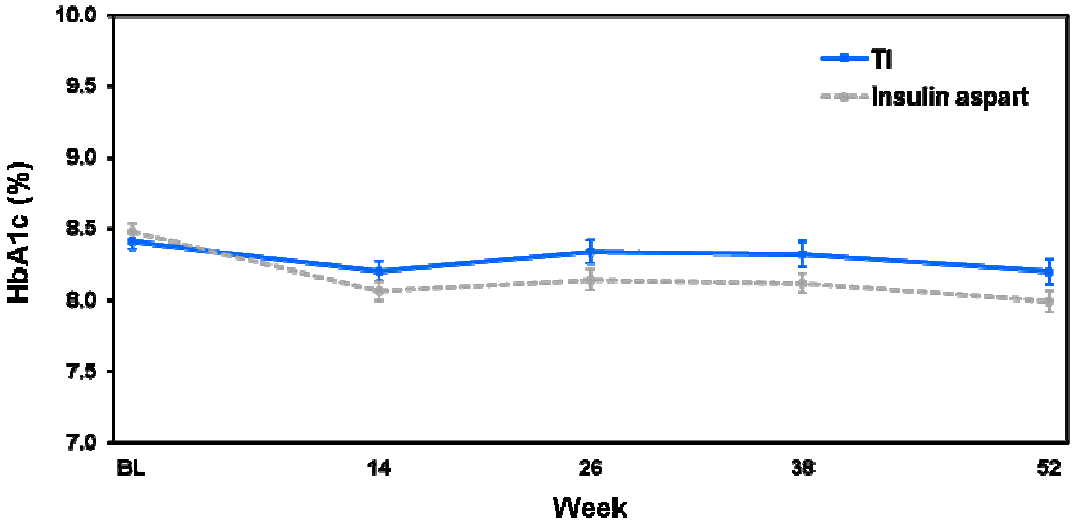
Figure 16: Mean (SE) HbA1c (%) Over 24 Weeks (Trial 171 FAS Population)



TI Gen2	172	152	146	142	132	131
Comparator	167	160	155	157	150	150

Error bar denotes ± standard errors.

Figure 17: Mean (SE) HbA1c (%) Over 52 Weeks (Trial 009 mITT Population with LOCF)



TI N:	277	272	224	210	202
Insulin aspart N:	262	259	238	235	219

Abbreviations: N1=number of subjects in the TI group, N2=number of subjects in the insulin aspart group.
Error bars denote ± 1 standard error.

In Trial 171, sensitivity analyses for the primary efficacy endpoint provided consistent results. Pattern mixture analysis demonstrated no significant difference in HbA1c changes

from baseline between trial completers and those that discontinued within each treatment group and also between the TI and insulin aspart groups. Examination of the interactions between the dropout patterns and treatments, dropout patterns and time (trial weeks), and the 3-way interaction of pattern, time (trial weeks), and trial treatment all yielded non-significant findings (p=0.1409, p=0.4220, and p=0.0752, respectively). These results indicated that missing HbA1c measurements did not affect the validity of the MMRM analysis of the primary trial endpoint in Trial 171.

Multiple Imputation (MI) analyses were also performed to evaluate the robustness of the noninferiority of TI compared with insulin aspart in Trial 171. Imputation was populated separately for each treatment group to carry the observed between-treatment HbA1c difference into the imputation. Such an approach is based on the null hypothesis and can be considered conservative against TI Gen2. A series of MI analyses was conducted:

- MI Analysis 1: The 0.4% margin was applied to Week 24 HbA1c for TI Gen2 subjects who discontinued due to dissatisfactory glucose control and were identified as potential Missing Not At Random (MNAR). This analysis assumed potential MNAR subjects to have inadequate glycemic control, even though dissatisfactory glycemic control is a subjective measure and these subjects did not necessarily have worse glycemic control compared with the rest of population.
- MI Analysis 2: Instead of penalizing the potential MNAR subjects, post-meal glucose was utilized as an additional predictor variable to reflect the exact treatment effect at the point of discontinuation. This analysis realistically imputed missing data according to the actual treatment response.
- MI Analysis 3: Imputation was performed assuming all discontinued subjects were missing at random (MAR). This served as a MAR sensitivity analysis for comparison with the original primary analysis (MMRM).

The upper bounds of the 95% CIs of the between-group differences from this series of MI analyses ranged from 0.38 to 0.39; these are similar to the result from the MMRM analysis and consistent with the noninferiority TI compared with insulin aspart.

Subgroup analyses were done retrospectively on the pooled datasets from Trials 171 and 009 for age and baseline BMI. Compared with overall results, similar patterns of HbA1c response were noted for ages <20, 20 to 40, >40 to 65, and >65 years between TI and comparator groups. For BMI categories of <25, 25 to <30, and ≥30, similar change from baseline HbA1c differences between TI and comparator were seen compared with the response in the overall population. A greater response in HbA1c was noted in subjects with BMI <25 in both treatment groups.

8.2.1.2 HbA1c Goal Attainment, FPG, and Weight Changes

Key secondary endpoints other than hypoglycemia are summarized for Trials 171 and 009 in Table 13. In Trial 171, more insulin aspart-treated subjects reached HbA1c targets of ≤7% and ≤6.5. In Trial 009, HbA1c goal attainment was similar in both treatment groups.

In both trials, the treatment differences in FPG decreases from baseline favored the TI group.

A consistent, clinically-relevant weight advantage was noted with TI versus insulin aspart therapy, both over a 24-week period (-1.32 kg between-group difference; Trial 171) and a 52-week period (-1.8 kg between-group difference; Trial 009). In both trials, subjects in the TI group lost weight while those in the insulin aspart group gained weight.

Table 13: Summary of Secondary Endpoints (HbA1c Goal Attainment, FPG, and Weight) in T1DM Trials

Trial	HbA1c Goal Attainment		Fasting Plasma Glucose (FPG)	Weight
MKC-TI-171				
TI + basal insulin	Week 24 HbA1c	% Subjects	Week 24 adjusted mean change (SE) from baseline: -25.27 (7.624) mg/dL	Week 24 adjusted mean change (SE) from baseline: -0.39 (0.438) kg; $p = 0.4955$
	≤ 7.0%	18.3%		
	≤ 6.5%	7.6%		
Comparator + basal insulin	Week 24 HbA1c	% Subjects	Week 24 adjusted mean change (SE) from baseline: 10.15 (7.396) mg/dL	Week 24 adjusted mean change (SE) from baseline: 0.93 (0.441) kg; $p = 0.0079$
	≤ 7.0%	30.7%		
	≤ 6.5%	12.7%		
TI versus Comparator	TI relative to Comparator: Week 24 HbA1c ≤ 7.0%: Odds ratio = 0.449; 95% CI: (0.23, 0.86); $p = 0.0158$ Week 24 HbA1c ≤ 6.5%: Odds ratio = 0.576; 95% CI: (0.24, 1.38); $p = 0.2144$		Treatment difference (TI – Comparator) Adjusted mean change (SE): -35.42 (10.622) mg/dL; 95% CI: (-56.25, -14.59) ; p=0.0009	Treatment difference (TI – Comparator) Adjusted mean change (SE): -1.32 (0.512) kg; 95% CI: (-2.33, -0.31); $p = 0.0102$

Table 13: Summary of Secondary Endpoints (HbA1c Goal Attainment, FPG, and Weight) in T1DM Trials

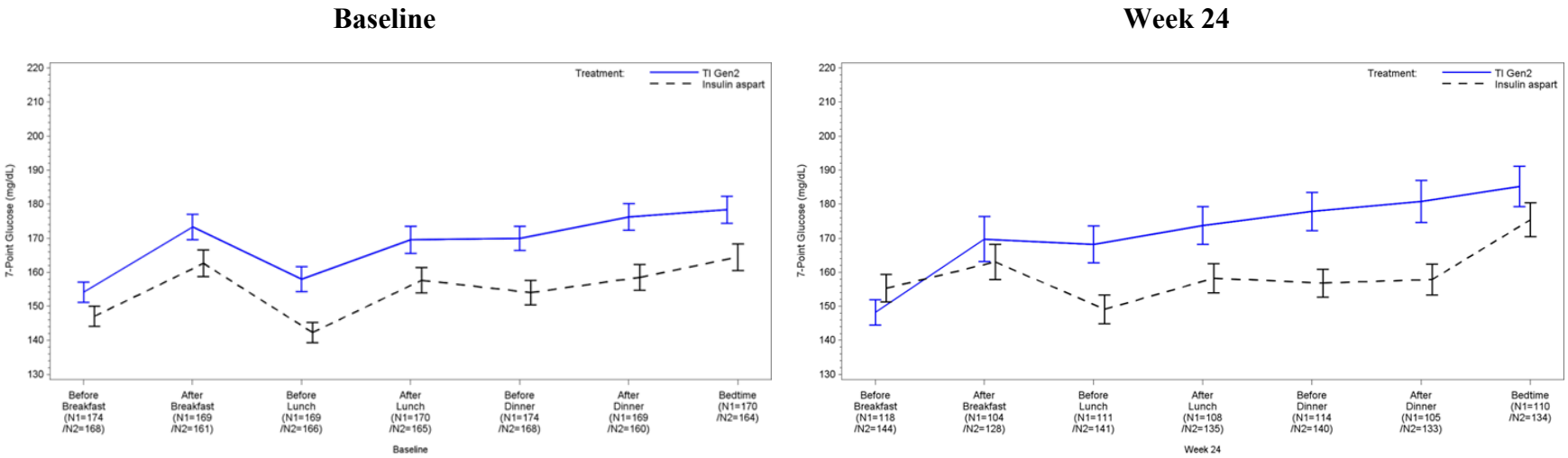
Trial	HbA1c Goal Attainment		Fasting Plasma Glucose (FPG)	Weight
Trial MKC-TI-009				
TI + basal insulin	Week 52 HbA1c	% Subjects	Week 52 adjusted mean change (SE) from baseline: -35.5 (3.33) mg/dL	Week 52 adjusted mean change (SE) from baseline: –0.5 (0.32) kg
	≤ 8.0%	51.0%		
	≤ 7.0%	16.3%		
	≤ 6.5%	7.4%		
Comparator + basal insulin	Week 52 HbA1c	% Subjects	Week 52 adjusted mean change (SE) from baseline: -20.6 (3.24) mg/dL	Week 52 adjusted mean change (SE) from baseline: 1.4 (0.30) kg
	≤ 8.0%	56.2%		
	≤ 7.0%	16.0%		
	≤ 6.5%	7.3%		
TI versus Comparator	TI relative to Comparator: Week 52 HbA1c ≤ 8.0%: Odds ratio = 0.658; 95% CI: (0.421, 1.028); p = 0.0661 Week 52 HbA1c ≤ 7.0%: Odds ratio = 0.941; 95% CI: (0.536, 1.652); p = 0.8311 Week 52 HbA1c ≤ 6.5%: Odds ratio = 0.942; 95% CI: (0.435, 2.039); p = 0.8785		Treatment difference (TI – Comparator) Adjusted mean change (SE): -14.8 (4.54) mg/dL; 95% CI: (-23.8, -5.9); p = 0.0012	Treatment difference (TI – Comparator) Adjusted mean change (SE): –1.8 (0.42) kg; 95% CI: (–2.7, –1.0); p = 0.0009;

Note: P-values for secondary endpoints are provided for descriptive purposes only because the approach for protecting Type 1 Error was either not fully pre-specified or an earlier stage in a step-down procedure was not passed.

8.2.1.3 Seven-Point Glucose Profiles

Figure 18 depicts the 7-point glucose profiles for both treatment groups at baseline and Week 24 in Trial 171. The baseline 7-point glucose profiles were higher at every time point for the TI group compared to the insulin aspart group; this treatment group imbalance was also seen at week 24, except for a lower pre-breakfast value in the TI group. A progressive increase in their SMBG values throughout the day was noted for both groups. At 24-weeks, the TI-treated group had a decrease in pre- to post-meal glucose excursions compared with baseline; this effect was not seen with insulin aspart. This resulted in a flatter prandial glycemic profile for TI compared with insulin aspart.

Figure 18: Seven-Point Glucose Profiles at Baseline and Week 24 in T1DM Subjects (Trial 171 FAS)



Abbreviations: FAS=full analysis set; N1=number of subjects in the TI group, N2=number of subjects in the insulin aspart group, T1DM=type 1 diabetes mellitus; TI=Technosphere Insulin.
Error bar denotes ± standard errors

8.2.1.4 Dosing

For Trial 171 (Table 14), the mean basal insulin doses in the TI group increased steadily from Week 1 through Week 12 and then remained relatively stable from Week 12 to Week 24, as directed by protocol. In the insulin aspart group, basal insulin doses were fairly stable throughout the treatment period. This was expected because the subjects randomized to insulin aspart simply continued the regimen they used in the run-in period.

Table 14: Mean (SD) Daily Basal Insulin (IU/Day) Doses during the Randomized Treatment Period in T1DM Trial 171 (Safety Population)

Week Post Randomization	TI (N=174)	Insulin Aspart (N=171)
Baseline	31.7 (15.0)	28.7 (17.4)
Week 4	33.5 (16.9)	29.5 (18.5)
Week 12	36.8 (20.4)	30.8 (20.3)
Week 24	37.1 (22.1)	31.6 (22.7)
Change from Baseline to Week 24	5.4	2.9

Abbreviations: IU=international units; SD=standard deviation.

Mean daily doses of prandial TI or prandial insulin aspart over the treatment period in Trial 171 are presented in Table 15. The TI dose increased from baseline to Week 12; from Week 12 to Week 24, the rate of increase was much less than during the first 12 weeks. As expected for subjects continuing the therapy used in the run-in period, the prandial insulin aspart dose remained stable throughout the 24-week treatment period.

Table 15: Mean (SD) Daily Prandial Insulin Doses during the Randomized Treatment Period in T1DM Trial 171 (Safety Population)

Week Post Randomization	TI (N=174)	Insulin Aspart (N=171)
Baseline	70.0 (33.3)	24.6 (12.9)
Week 4	98.6 (52.6)	24.6 (12.4)
Week 8	105.9 (55.1)	26.0 (13.3)
Week 12	107.4 (59.0)	25.6 (12.6)
Week 24	115.4 (63.2)	25.9 (14.1)
Change from Baseline to Week 24	45.4	1.3

Note: The TI Gen2 doses are given in cartridge fill units. The comparator (insulin aspart) doses are given in IUs. Baseline TI doses are presented as TI Units converted from the insulin aspart dose at the end of the run-in period (28.01 [SD 13.30]), utilizing a 4-unit conversion factor that was used to convert subjects from RAA aspart insulin to TI dosing.

In Trial 009, the mean daily TI dose increased by approximately 85 U (fill content of TI cartridges) from baseline to the end of the 52-week treatment period (Table 16). The mean daily insulin aspart dose increased by approximately 4 units during the 52-week treatment period. Basal insulin doses were similar between treatment groups and did not change much throughout the trial (Table 17).

Table 16: Mean (SD) Daily Basal Insulin (IU/Day) Doses during the Randomized Treatment Period in T1DM Trial 009 (Safety Population)

Week Post Randomization	TI (N=293)	Insulin Aspart (N=272)
Baseline	28.0 (20.6)	28.9 (12.6)
Week 12	33.2 (24.1)	30.0 (12.7)
Week 24	32.9 (23.9)	29.9 (13.1)
Week 52	32.8 (17.4)	30.4 (13.6)
Change from Baseline to Week 52	4.8	1.5

Table 17: Mean (SD) Daily Prandial Insulin Doses during the Randomized Treatment Period in T1DM Trial 009 (Safety Population)

Week Post Randomization	TI (N=293)	Insulin Aspart (N=272)
Baseline	72.0 (31.7)	26.7 (28.6)
Week 12	147.7 (70.1)	30.8 (29.4)
Week 24	148.4 (65.8)	29.2 (16.5)
Week 52	156.7 (64.0)	30.6 (21.4)
Change from Baseline to Week 52	84.7	3.9

Note: The TI doses are given in cartridge fill units. The comparator (insulin aspart) doses are given in IUs.
Baseline TI doses are presented as TI Units converted from the prandial insulin dose at trial entry, utilizing a 5-unit conversion factor used to convert subjects from pre-trial insulin to TI dosing.

8.2.2 Type 2 Diabetes Mellitus (Trials 175 and 102)

8.2.2.1 HbA1c Change from Baseline (Primary Efficacy Endpoint)

Results for HbA1c change from baseline to the end of treatment are presented in Table 18 and Figure 19.

In Trial 175, at randomization, the adjusted mean baseline HbA1c levels were comparable between treatment groups (8.25%, TI; 8.27% TP [placebo]). TI administration resulted in a significantly greater change in HbA1c from baseline compared with TP (Week 24 HbA1c adjusted mean changes from baseline of -0.82% and -0.42%, respectively). TI was superior to placebo in HbA1c change from baseline (between-group difference -0.40% [95%CI -0.57, -0.23; $p<0.0001$]; Table 18). However, both treatment groups (TI and TP) achieved clinically-significant HbAlc reduction. These results for the placebo group may have been influenced by increased glycemic control awareness due to the new/increased BG self-monitoring and consequent lifestyle/diet changes; lack of a notable mealtime glucose response to an inhaled drug (placebo) despite increased dosing (Table 20) may have been a strong additional motivating factor for such change.

In Trial 102 both treatment groups (basal insulin [glargine]/TI and BPR 70/30 bid) had comparable mean adjusted baseline HbA1c levels (8.69% for TI; 8.68% for BPR 70/30) with adjusted mean changes from baseline of -0.59% and -0.71% at 52 weeks, respectively. Noninferiority of TI plus basal insulin to BPR 70/30 bid was demonstrated (between-group difference 0.12% [95%CI -0.05, 0.29]) (Table 18).

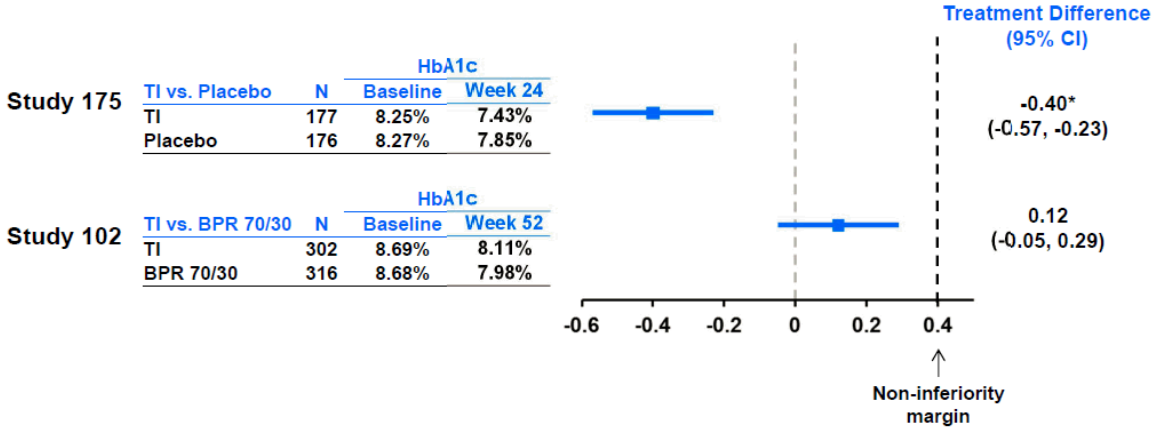
Table 18: HbA1c (%) Change from Baseline in T2DM Trials

HbA1c Statistics	TI	Comparator	Treatment Difference TI – comparator
Trial MKC-TI-175[a] Week 24			
Number of Subjects	177	176	
Baseline HbA1c (%)	8.25	8.27	
Adjusted Mean Change (SE), %	-0.82 (0.061)	-0.42 (0.062)	-0.40 (0.087)
95% CI			(-0.57, -0.23)
p-value			< 0.0001
Trial MKC-TI-102[b] Week 52			
Number of Subjects	302	316	
Baseline HbA1c (%)	8.69	8.68	
Adjusted Mean Change (SE), %	-0.59 (0.063)	-0.71 (0.061)	0.12 (0.085)
95% CI	(-0.71, -0.47)	(-0.83, -0.59)	(-0.05, 0.29)

a: For Trial MKC-TI-175, TI inhaler: Gen2; comparator: TP (placebo); analysis population: FAS; primary analysis of change from baseline at Week 24 in HbA1c (%): MMRM

b: For Trial MKC-TI-102, TI inhaler: MedTone; comparator: BPR 70/30; analysis population: mITT Population; primary analysis of change from baseline in HbA1c (%) at Week 52: ANCOVA with LOCF

Figure 19: Between Group Differences in HbA1c (%) Change from Baseline to End of Treatment in T2DM Trials

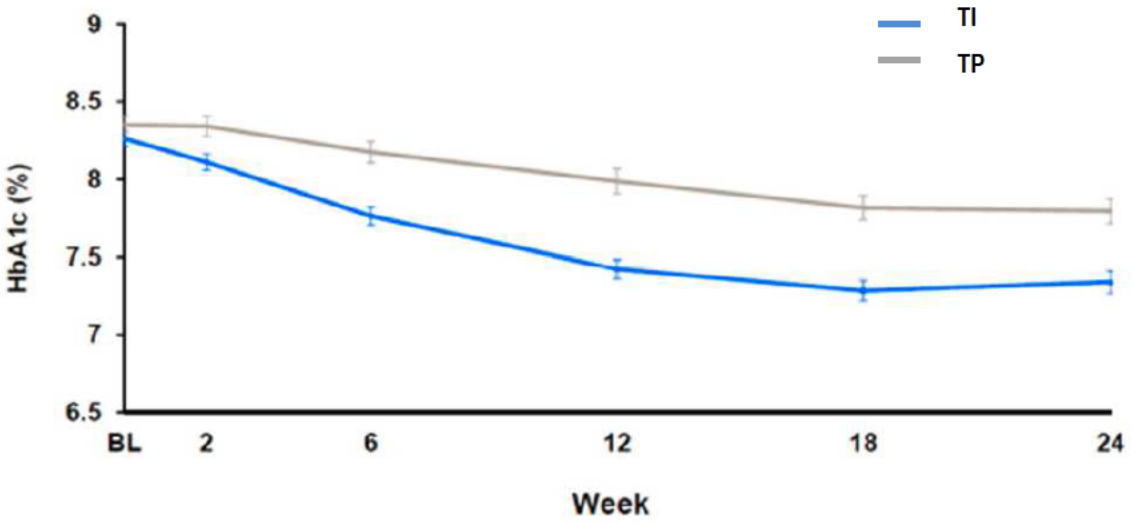


*p < 0.0001
Notes: Graph shows point estimate and 95% CI of the between group difference (TI minus comparator). Baseline is model-adjusted.

Figure 20 and Figure 21 depict mean HbA1c change over time achieved in the Trials 175 and 102.

In Trial 175, the observed mean HbA1c levels at Screening were 8.64% and 8.68% for the TI and TP groups, respectively. These values declined by 0.38% and 0.33% for TI and TP groups, respectively, during the 6-week run-in period. After randomization, TI administration resulted in an early and sustained decline in HbA1c, with an increasing between-group difference noted over time. HbA1c change from baseline in the TI group was -0.79% and -0.82% at Weeks 12 and 24, respectively (Figure 20), consistent with protocol requirements of steady dosing for the last half of the trial. The placebo group had a fairly continuous decrease in HbA1c levels throughout the trial (-0.30% and -0.42% change from baseline at Weeks 12 and 24); however, HbA1c decreased at a slower trajectory during the last half of the trial.

Figure 20: Mean (SE) HbA1c (%) Over 24 Weeks (Trial 175 FAS Population)

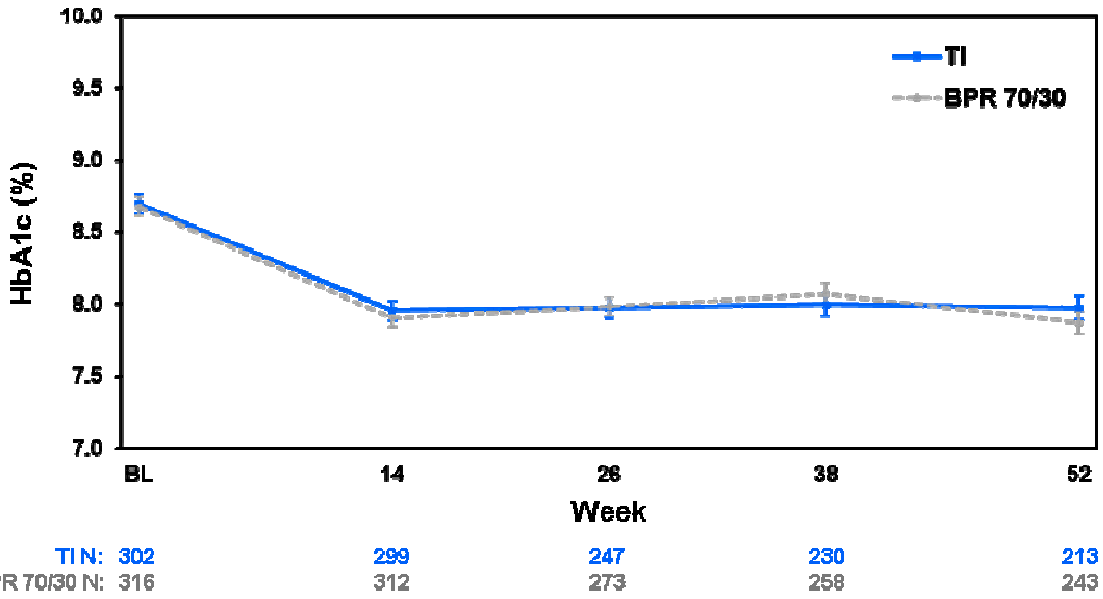


TI Gen2	176	174	163	159	149	139
Comparator	176	167	163	147	137	129

Error bar denotes ± SE. Note: Comparator was TP (Technosphere particles [placebo, no insulin]).

In Trial 102, the TI and BPR 70/30 groups had very similar patterns of glycemic response (Figure 21). A maximal effect was noted by Week 14 for both treatment groups (-0.74% for TI and -0.77% for BPR 70/30); the effect was sustained for the duration of the 52-week trial in both groups.

Figure 21: Mean (SE) HbA1c (%) Over 52 Weeks (Trial 102 mITT Population)



TI group received TI + basal insulin; BPR 70/30 was dosed bid.

Sensitivity analyses were conducted for both Trials 175 and 102. In Trial 175, according to pattern mixture analysis, the interaction between dropout pattern and time and/or treatment analyses showed that subjects who completed the trial had larger HbA1c decreases compared with those who did not complete the trial; however, the trends were the same for both treatment groups. The interaction between dropout pattern and time (week) was statistically significant (p=0.0015), but the interaction between pattern and treatment group and the 3-way interaction of pattern, time, treatment were not statistically significant. The analysis supported the conclusion that the missing HbA1c measurements did not affect the validity of the primary efficacy results. In addition, multiple sensitivity analyses (including an analysis that was based on all HbA1c data collected regardless of whether or not the visit occurred after the initiation of rescue therapy) confirmed the superiority of TI versus placebo ($p<0.0001$ for all the sensitivity analyses). In Trial 102, ANCOVA was also performed on the PP population and MMRM was performed on the mITT and PP populations. The results of these 3 analyses were consistent with the primary analysis in showing noninferiority of TI plus basal insulin compared with BPR 70/30. In addition, for Trial 175, data collected after rescue therapy was also included in a sensitivity analysis and the result was consistent with primary analysis.

Subgroup analyses were done retrospectively on the pooled datasets for Week 24 data from Trials 175 and 102 for age and baseline BMI. Compared with overall results, similar patterns of HbA1c response were noted for age >65 years between TI and comparator; for 20-40 and >40-65 age groups, HbA1c change from baseline appeared similar or even slightly greater in TI relative to comparator. For BMI categories of <25, 25 to <30, and ≥30, similar change from baseline HbA1c differences were seen between TI and comparator compared with the response in the overall population. A greater response in HbA1c was noted in subjects with BMI <25 in both treatment groups.

8.2.2.2 HbA1c Goal Attainment, FPG, and Weight Changes

Key secondary endpoints other than hypoglycemia are summarized for Trials 175 and 102 in Table 19.

In Trial 175, a greater percentage of subjects reached each pre-specified HbA1c goal in the TI group than in the TP (placebo) group. Nearly 40% of T2DM subjects were at or below HbA1c 7% by the end of the trial with twice as many attaining ADA treatment target than the control group. Four times as many TI-treated subjects reached an end-of-trial HbA1c ≤6.5%, although the numbers reaching that target were relatively small. In Trial 102, approximately the same percentage of subjects in both groups reached each HbAlc goal.

A greater reduction in FPG was seen with TI plus basal insulin compared to BPR 70/30 bid therapy in Trial 102.

A modest weight gain (0.49 kg) was noted in the TI group over the 24-week duration of Trial 175; the placebo group lost -1.13 kg, and the between-group treatment difference favored placebo (1.62 kg). In Trial 102, less weight gain was seen with TI versus BPR 70/30, with a between-treatment difference of -1.6 kg.

Table 19: Summary of Secondary Endpoints (HbA1c Goal Attainment, FPG, and Weight) in T2DM Trials

Trial	HbA1c Goal Attainment		Fasting Plasma Glucose (FPG)	Weight
MKC-TI-175				
TI + OADs	Week 24 HbA1c	% Subjects	Week 24 adjusted mean change (SE) from baseline: -11.20 (3.776) mg/dL	Week 24 adjusted mean change (SE) from baseline: 0.49 (0.333) kg; $p = 0.0060$
	≤ 7.0%	37.7%		
	≤ 6.5%	15.9%		
TP + OADs	Week 24 HbA1c	% Subjects	Week 24 adjusted mean change (SE) from baseline: -3.78 (3.864) mg/dL	Week 24 adjusted mean change (SE) from baseline: -1.13 (0.347) kg; $p = 0.0001$
	≤ 7.0%	19.0%		
	≤ 6.5%	4.2%		
TI versus TP	TI relative to TP (placebo): Week 24 HbA1c ≤ 7.0%: Odds ratio = 2.726; 95% CI: (1.55, 4.80); $p = 0.0005$ Week 24 HbA1c ≤ 6.5%: Odds ratio = 4.361; 95% CI: (1.70, 11.17); $p = 0.0021$		Treatment difference (TI – placebo) Adjusted mean change (SE): -7.42 (5.400) mg/dL; 95% CI: (-18.03, 3.18); $p = 0.1698$	Treatment difference (TI – placebo) Adjusted mean change (SE): 1.62 (0.365) kg; 95% CI: (0.90, 2.34); $p < 0.0001$

Table 19: Summary of Secondary Endpoints (HbA1c Goal Attainment, FPG, and Weight) in T2DM Trials

Trial	HbA1c Goal Attainment		Fasting Plasma Glucose (FPG)	Weight
Trial MKC-TI-102				
TI + basal insulin	Week 52 HbA1c	% Subjects	Week 52 adjusted mean change (SE) from baseline: -26.7 (2.69) mg/dL	Week 52 adjusted mean change (SE) from baseline: 0.9 (0.32) kg; 95% CI: (0.3, 1.5); $p = 0.0056$
	≤ 8.0%	56.8%		
	≤ 7.0%	22.1%		
	≤ 6.5%	8.0%		
BPR 70/30	Week 52 HbA1c	% Subjects	Week 52 adjusted mean change (SE) from baseline: -12.9 (2.56) mg/dL	Week 52 adjusted mean change (SE) from baseline: 2.5 (0.29) kg; 95% CI: (1.9, 3.0); $p < 0.0001$
	≤ 8.0%	60.9%		
	≤ 7.0%	26.8%		
	≤ 6.5%	12.4%		
TI versus Comparator	TI relative to Comparator: Week 52 HbA1c ≤ 8.0%: Odds ratio = 0.862; 95% CI: (0.580, 1.282); $p = 0.4642$ Week 52 HbA1c ≤ 7.0%: Odds ratio = 0.774; 95% CI: (0.486, 1.231); $p = 0.2793$ Week 52 HbA1c ≤ 6.5%: Odds ratio = 0.608; 95% CI: (0.318, 1.163); $p = 0.1328$		Treatment difference (TI – Comparator) Adjusted mean change (SE): -13.8 (3.58) mg/dL; 95% CI: (-20.8, -6.7); $p = 0.0001$	Treatment difference (TI – Comparator) Adjusted mean change (SE): –1.6 (0.41) kg; 95% CI: (-2.4 ,-0.7); $p = 0.0002$

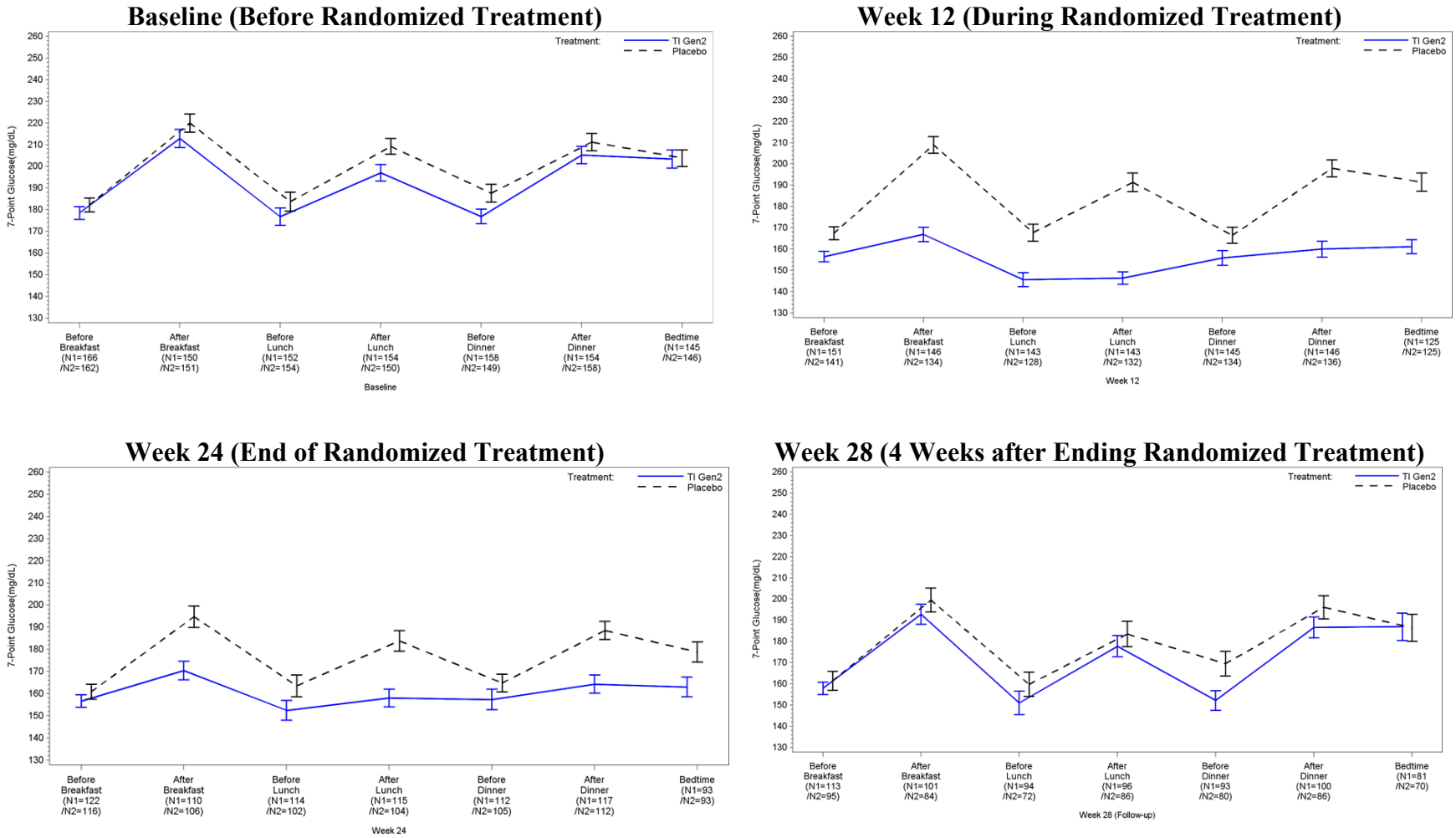
Note: P-values for secondary endpoints are provided for descriptive purposes only because the approach for protecting Type 1 Error was either not fully pre-specified or an earlier stage in a step-down procedure was not passed.

8.2.2.3 Seven-Point Glucose Profiles

Figure 22 shows the mean 7-point glucose measurements over time at baseline, on-treatment (Week 12 and Week 24), and 4 weeks after completion of therapy for TI subjects and placebo subjects in Trial 175. Although formal statistical comparisons were not performed, a descriptive comparison suggests that TI-treated subjects had improved 7-point glucose profiles with reduced postprandial glucose excursions compared with baseline at Week 12 and Week 24. The mean postprandial glucose levels in the TI group at all timepoints were numerically lower compared to baseline and placebo comparator levels. At Week 28 (4 weeks after the end of treatment), the mean 7-point glucose profiles appeared similar to the baseline profiles for the TI group.

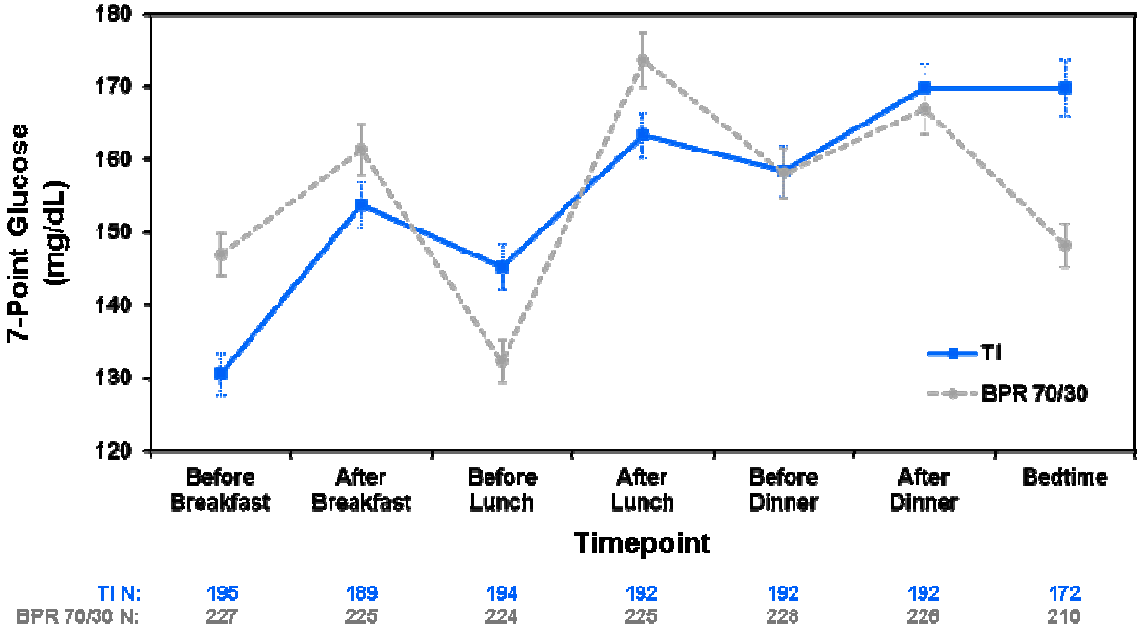
Figure 23 depicts the 7-point glucose levels for both treatment groups in Trial 102 at the end of the 52-week treatment period. A greater glycemic excursion after lunch was noted in the BPR 70/30 group, consistent with the known time-action profile of pre-mix insulin. The bedtime glucose values were higher in the TI group, reflecting the different kinetics for the basal components of each regimen (single daily dose of insulin glargine versus twice daily insulin aspart protamine).

Figure 22: Seven-Point Glucose Profiles at Various Timepoints in T2DM Subjects (Trial 175 FAS Population)



Error bar denotes ± standard errors

Figure 23: Seven-Point Glucose Profile at Week 52 in T2DM Subjects (Trial 102 mITT Population)



Error bar denotes ± standard errors

8.2.2.4 Dosing

For Trial 175, the mean daily TI and TP doses during the treatment period are shown in Table 20. "TP doses" are available because the subjects and investigators treated TP (placebo) as if it were TI because of the double-blind design. All subjects were started on 10 U of TI or TP per meal per day. The average daily dose of TI as well as TP increased in the first 12 weeks (dose titration) and then stabilized in the last 12 weeks (stable dosing). The average daily dose during stable dosing was substantially higher in the TP group than the TI group. Twelve (6.8%) subjects in the TI group and 17 (9.7%) subjects in the TP group received rescue therapy during the study.

Table 20: Mean (SD) Daily Dose of TI (Cartridge Fill Units) during the Treatment Period in T2DM Trial 175 (Safety Population)

Week Post Randomization	TI (N=177)	TP (N=176)
Baseline	NA	NA
Week 4	67.4 (28.9)	77.6 (34.0)
Week 8	94.6 (45.8)	123.7 (61.9)
Week 12	109.4 (57.5)	164.0 (83.6)
Week 24	115.0 (65.1)	169.4 (97.2)

Abbreviations: NA = not applicable.

Total daily doses of TI and BPR 70/30 for Trial 102 are depicted in Table 21. In both treatment groups, a rapid titration of insulin occurred early in the trial and then slowed considerably, with insulin doses maintained reasonably unchanged over the last 6 months of the trial.

Table 21: Mean (SD) Total Daily Doses of Basal Insulin (IU), TI (U), and BPR 70/30 (IU) by Time after Randomization (Trial 102 Safety Population)

	TI Group (N=323)		BPR 70/30 Group (N=331)
Time Post Randomization	**Basal Insulin**	**TI**	**Total Insulin**
Baseline	31.5 (14.1)	79.4 (40.1)	61.2 (34.7)
Week 12	43.7 (22.6)	187.8 (67.2)	81.2 (42.5)
Week 24	43.9 (23.0)	188.2 (68.7)	82.8 (43.8)
Week 52	47.2 (25.7)	194.6 (68.9)	87.9 (47.0)
Change from Baseline to Week 52	15.7	115.2	26.7

Average Daily Dose is defined as the sum of (daily doses)/day's trial treatment was taken.

The dosage unit in the TI + basal insulin group is U (TI cartridge fill content) and the dosage unit in the BPR 70/30 group is IU of insulin.

Baseline TI doses are presented as TI Units converted from the prandial insulin dose at trial entry, utilizing a 5-unit conversion factor used to convert subjects from pre-trial insulin to TI dosing.

8.3 Hypoglycemia in Both Types of Diabetes Mellitus

Both T1DM and T2DM subjects on TI experienced lower incidence and event rates of hypoglycemia compared with subjects on an insulin comparator. This hypoglycemia advantage for TI-treated subjects was maintained throughout the treatment period and remained when hypoglycemia rates were adjusted for attained HbA1c levels.

8.3.1 Type 1 Diabetes Mellitus

8.3.1.1 Trial 171

The event rates for hypoglycemia during the treatment period are presented in Table 22 for Trial 171. Subjects in the TI group experienced less hypoglycemia across all categories of hypoglycemia severity than subjects in the insulin aspart group. TI event rates for severe hypoglycemia were 44.3% lower (8.05 [TI] versus 14.45 [Comparator] events per 100 subject-months). The lower incidence rates of hypoglycemia for the TI group were maintained throughout the treatment period (Figure 24).

In subjects who had a hypoglycemic event rate ≥ the median during the run-in period, those subsequently randomized to TI had a lower event rate (8.59 per 100-subject month) for overall hypoglycemia during randomized treatment compared with subjects randomized to insulin aspart (19.86 per 100 subject-month; p=0.0462). A post-hoc analysis of the temporal relationship between hypoglycemic events and mealtimes was performed, to better assess interprandial hypoglycemic rates. Hypoglycemic event rates per subject-month for the time periods ≤2 hours and >2-5 hours after start of a meal were 2.9 and 2.1 for TI subjects, and 3.4

and 5.1 for insulin aspart subjects, respectively. These results are consistent with the more rapid kinetics of TI compared to insulin aspart.

Despite a lower FPG, TI-treated subjects did not have a higher incidence or event rate of either all or severe nocturnal hypoglycemia (midnight to 6 am). In the TI group, 74.1% of subjects experienced any nocturnal hypoglycemia and 5.2% experienced severe nocturnal hypoglycemia; corresponding incidence rates in the comparator group were 81.9% and 6.4%, respectively. Event rates in the TI group for all nocturnal hypoglycemia and severe nocturnal hypoglycemia were 1.05 per subject-month and 1.86 per 100 subject-months, respectively; corresponding event rates in the comparator group were 1.51 per subject-month and 2.45 per 100 subject-months, respectively.

The lower event rates of hypoglycemia for the TI group were evident when analyzed by attained HbA1c target categories for severe (Figure 25) and mild/moderate (Figure 26) hypoglycemia. In both figures, it is clear that the reduction of severe hypoglycemia, as well as the reduction in mild/moderate hypoglycemia, in the TI group relative to the insulin aspart group is consistent regardless of the HbA1c response achieved at Week 24.

Table 22: Hypoglycemic Incidence and Event Rates during the Treatment Period in T1DM Trial 171 (Safety Population)

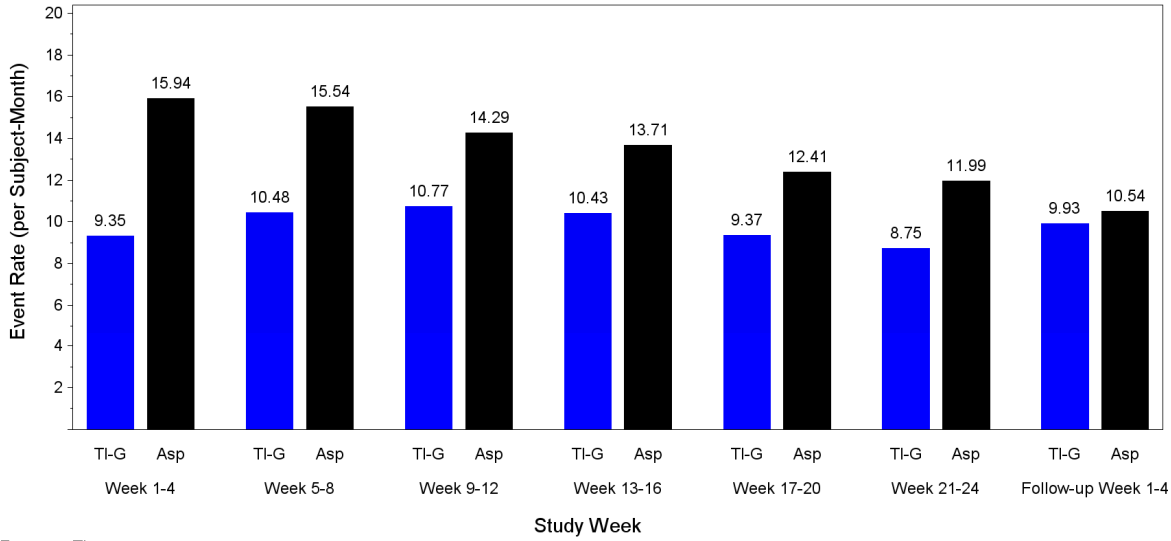
Category	TI Gen2 (N=174)	Comparator (N=171)	TI - Comparator p-Value[a]
All Hypoglycemia			
Number of Subjects at Risk	174	171	
Number of Subjects with Events (%)[b]	167 (96.0)	170 (99.4)	
Number of Events	7919	12571	
Exposure Time in Subject-Month	807.7	899.6	
Event Rate (per Subject-Month)[c]	9.80	13.97	<0.0001
Mild or Moderate Hypoglycemia			
Number of Subjects at Risk	174	171	
Number of Subjects with Events (%)[b]	166 (95.4)	170 (99.4)	
Number of Events	7854	12441	
Exposure Time in Subject-Month	807.7	899.6	
Event Rate (per Subject-Month)[c]	9.72	13.83	<0.0001
Severe Hypoglycemia			
Number of Subjects at Risk	174	171	
Number of Subjects with Events (%)[b]	32 (18.4)	50 (29.2)	0.0156
Number of Events	65	130	
Exposure Time in Subject-Month	807.7	899.6	
Event Rate (per 100-Subject-Month)[c]	8.05	14.45	0.1022
Hypoglycemia with Glucose ≤ 36 mg/dL			
Number of Subjects at Risk	174	171	
Number of Subjects with Events (%)[b]	41 (23.6)	63 (36.8)	0.0062
Number of Events	94	230	
Exposure Time in Subject-Month	807.7	899.6	
Event Rate (per 100-Subject-Month)[c]	11.64	25.57	0.0009

a: p-Value is from a negative binomial regression analysis with terms for region, basal insulin stratum, and treatment in the model with duration of treatment exposure as an offset.

b: Percentage is calculated based on the total number of subjects at risk for each time interval. Subject could have more than one event in a day.

c: Event rate = Total number of events / total exposure time in subject-month.

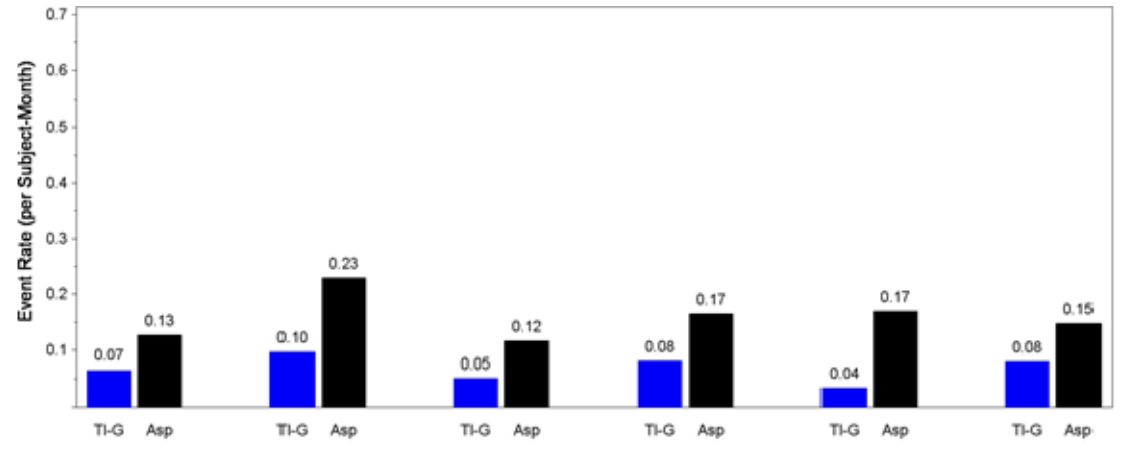
Figure 24: Total Hypoglycemia Event Rates over Time in T1DM Trial 171 (Safety Population)



Exposure Time:							
TI Gen2:	152.4	138.5	133.3	126.1	124.2	118.2	117.9
Insulin aspart:	154.6	151.6	148.4	144.5	143.4	138.5	138.5
Number of events:							
TI Gen2:	1425	1452	1435	1315	1164	1034	1170
Insulin aspart:	2464	2356	2120	1982	1780	1660	1460

Note: Event rates are presented per subject-month.

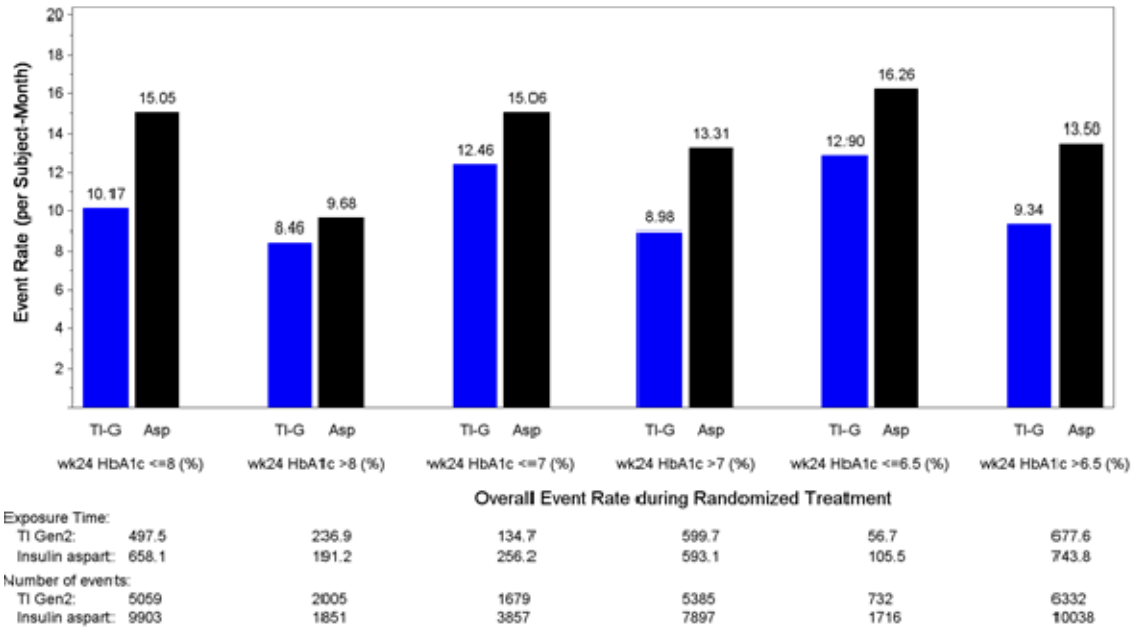
Figure 25: Severe Hypoglycemia Event Rates by Week 24 HbA1c in T1DM Trial 171 (Safety Population)



Exposure Time:						
TI Gen2:	497.5	236.9	134.7	599.7	56.7	677.6
Insulin aspart:	658.1	191.2	256.2	593.1	105.5	743.8
Number of events:						
TI Gen2:	33	23	7	49	2	54
Insulin aspart:	84	44	30	98	18	110

Note: Event rates are presented per subject-month.

Figure 26: Mild/Moderate Hypoglycemia Event Rates by Week 24 HbA1c in T1DM Trial 171 (Safety Population)



Exposure Time:						
TI Gen2:	497.5	236.9	134.7	599.7	56.7	677.6
Insulin aspart:	658.1	191.2	256.2	593.1	105.5	743.8
Number of events:						
TI Gen2:	5059	2005	1679	5385	732	6332
Insulin aspart:	9903	1851	3857	7897	1716	10038

Note: Event rates are presented per subject-month.

To further assess the impact on the hypoglycemia event rate of the small, between-group differences in HbA1c, an additional analysis was carried out in which end of study HbA1c and the associated change from baseline in HbA1c were included in the negative binomial regression model as further explanatory variables. Both the original analysis and this additional analysis allow for any difference in treatment duration by including treatment exposure time as an offset. As shown in Table 23, with the original model (which does not include terms related to HbA1c), TI reduces the adjusted event rate for total hypoglycemia by 31.6% and reduces the adjusted event rate for severe hypoglycemia by 37.0%. With the revised model (which includes further terms that adjust for the impact of treatment on HbA1c), TI reduces the adjusted event rate for total hypoglycemia by 26.8% and reduces the adjusted event rate for severe hypoglycemia by 43.2%.

The above results show that the small, between-group difference in HbA1c favoring the insulin aspart arm is not the reason for the beneficial effect on hypoglycemia seen with TI. Even after adjusting for the impact of treatment on HbA1c, large and clinically relevant reductions in both total hypoglycemia and severe hypoglycemia event rates are still seen.

Table 23: Hypoglycemic Event Rates during the Treatment Period in T1DM Trial 171 – Results from Models with and without Terms for the Effect of Treatment on HbA1c (Safety Population)

	TI Gen2 (N=174)	Comparator (N=171)	Percentage Reduction in Event Rate	TI - Comparator p-Value
Adjusted Event Rate from the Original Model[a] (per 100 Subject-Months)				
Total Hypoglycemia	1028	1503	31.6%	<0.0001[a]
Severe Hypoglycemia	8.84	14.03	37.0%	0.1022[a]
Adjusted Event Rate from the Model with Additional HbA1c terms[b] (per 100 Subject-Months)				
Total Hypoglycemia	1035	1414	26.8%	<0.0001[b]
Severe Hypoglycemia	8.66	15.24	43.2%	0.0516[b]

a: Adjusted event rates and p-values from a negative binomial regression analysis with terms for region, basal insulin stratum, and treatment in the model with duration of treatment exposure as an offset. The event rates given in this table are model-adjusted, whereas the event rates given in Table 22 are based on the total number of events divided by the total exposure time.

b: Adjusted event rates and p-values from a negative binomial regression analysis with terms for region, basal insulin stratum, treatment, HbA1c change from baseline, and HbA1c at end of treatment in the model with duration of treatment exposure as an offset.

8.3.1.2 Trial 009

In Trial 009, fewer TI subjects experienced hypoglycemic events (any severity) compared with comparator insulin aspart subjects (odds ratio = 0.488, p=0.0124). Numerically fewer TI subjects experienced severe hypoglycemic events compared with comparator (odds ratio = 0.812, p=0.2387). The event rate for any hypoglycemia (events per subject month) was similar between the treatment groups (1.81 for TI versus 1.85 for comparator, p=0.1094). The event rate for severe hypoglycemia (0.08 events/100 subject-months for TI versus 0.10 for comparator) was also similar for the treatment groups (p=0.1839).

8.3.1.3 Serious TEAEs of Hypoglycemia in T1DM Subjects

Table 24 summarizes serious TEAEs of hypoglycemia in T1DM subjects in the pooled Phase 2/3 trial 2013 Resubmission Safety Population. The incidence of a hypoglycemia SAE was 4.0% for the TI group and 4.8% for the comparator group. Hypoglycemic events reported as SAEs in the nervous system disorder system organ class (SOC) were similar between TI and comparator groups. In Trial 171, serious TEAEs related to hypoglycemia were reported in 3 subjects in the TI Gen2 group and 4 subjects in the insulin aspart group (Appendix 6). In Trial 009, SAEs related to hypoglycemia were reported with an incidence of 34/293 (11.6%) and 34/272 (12.5%) for the TI and insulin aspart groups, respectively.

Table 24: Serious TEAEs of Hypoglycemia in T1DM Subjects (2013 Resubmission Safety Population)

System Organ Class Preferred Term	TI [N=1026] SYE=697 n (%)	Comparator [N=835] SYE=778 n (%)
Metabolism and nutrition disorders	56 (5.5)	47 (5.6)
Hypoglycaemia	41 (4.0)	40 (4.8)
Nervous system disorders	22 (2.1)	15 (1.8)
Hypoglycaemic unconsciousness	7 (0.7)	4 (0.5)
Hypoglycaemic seizure	5 (0.5)	6 (0.7)
Hypoglycaemic coma	0 (0.0)	1 (0.1)
Loss of consciousness	9 (0.9)	6 (0.7)

Note: Each subject was counted only once per system organ class and preferred term combined. Percentages were based on the number of subjects in each treatment group in the Safety Population.

Note: SAEs designated as “loss of consciousness' or 'hypoglycemic unconsciousness' were associated with severe hypoglycemia.

8.3.2 Type 2 Diabetes Mellitus

8.3.2.1 Trial 175

Table 25 depicts the hypoglycemia incidences and event rates by severity category for TI subjects compared to TP (placebo) subjects. The event rate for hypoglycemia (any severity) was higher for TI versus TP groups. The incidence for severe hypoglycemic events was low in both groups.

Table 25: Hypoglycemic Event Rates during the Treatment Period in T2DM Trial 175 (Safety Population)

Category	TI (N=177)	TP (Placebo) (N=176)	TI - Placebo *P*-value[a]
All Hypoglycemic Events			
Number of Subjects at Risk	177	176	
Number of Subjects with Events (%)[b]	120 (67.8)	54 (30.7)	<0.0001
Number of Events	1030	417	
Exposure Time in Subject-Month	885.1	834.1	
Event Rate (per Subject-Month)	1.16	0.50	<0.0001
Severe Hypoglycemic Events			
Number of Subjects at Risk	177	176	
Number of Subjects with Events (%)[b]	9 (5.1)	3 (1.7)	0.0943
Number of Events	21	5	
Exposure Time in Subject-Month	885.1	834.1	
Event Rate (per 100 Subject-Month)	2.37	0.60	0.2024

Table 25: Hypoglycemic Event Rates during the Treatment Period in T2DM Trial 175 (Safety Population)

Category	TI (N=177)	TP (Placebo) (N=176)	TI - Placebo *P*-value[a]
Hypoglycemic Events with Glucose ≤ 36 mg/dL			
Number of Subjects at Risk	177	176	
Number of Subjects with Events (%)[b]	3 (1.7)	2 (1.1)	0.6711
Number of Events	6	2	
Exposure Time in Subject-Month	885.1	834.1	
Event Rate (per 100 Subject-Month)	0.68	0.24	0.4684

Note(s):
a: *P*-value is from a negative binomial model with terms of treatment, region and pooled OAD stratum in the model and exposure time as an offset variable.
b: Percentage is calculated based on the total number of subjects at risk for each time interval.
Event rate = Total number of events / total exposure time in subject-month. Subject can have more than one event in a day.

The use of exogenous insulin with insulin secretagogues is associated with an increased risk for hypoglycemia in patients with T2DM. Therefore, a post-hoc analysis with respect to background OAD use was done to assess hypoglycemia event rates for TI or placebo treatment groups in subjects receiving metformin alone versus subjects receiving both metformin and sulfonylurea (SU). Results are presented in Table 26. As expected, hypoglycemia event rates were higher in the metformin + SU population compared with the metformin alone population for both treatment groups with 2-fold and 6-fold increases in hypoglycemia event rates noted for TI and placebo groups, respectively. However, the hypoglycemia event rate in TI subjects receiving only metformin was 0.62 per subject-month, not appreciably different from the 0.68 per subject-month event rate seen in placebo subjects receiving metformin + SU, a frequently-used two-drug combination in clinical practice.

Table 26: Hypoglycemia in T2DM Subjects Receiving Metformin Only or Metformin Plus SU as OAD Therapy (Trial 175)

Category	TI	TP (Placebo)
Metformin Only		
Number Subjects at Risk	42	40
Number (%) Subjects with Hypoglycemia	22 (52.4)	9 (22.5)
Total Number of Events	120	20
Exposure (subject-months)	194.1	188.6
Event Rate (events/per subject-month)	0.62	0.11
Metformin + SU		
Number Subjects at Risk	114	115
Number (%) Subjects with Hypoglycemia	83 (72.8)	39 (33.9)
Total Number of Events	782	380
Exposure (subject-months)	587.8	558.1
Event Rate (events/per subject-month)	1.33	0.68

8.3.2.2 Trial 102

In Trial 102, TI was associated with decreased hypoglycemia incidence and event rates across most categories of severity compared to BPR 70/30 (Table 27). TI was associated with a 32.8% and 65% reduction in event rates for all and severe hypoglycemia, respectively.

Table 27: Hypoglycemic Incidence and Event Rates during the Treatment Period in T2DM (Trial 102 Safety Population)

	TI (N = 323)	BPR 70/30 (N = 331)	TI – Comparator P-value[a]
All Hypoglycemia			
Number of Subjects at Risk	323	331	
Number of Subjects with Events (%)[b]	155 (47.99)	228 (68.88)	<0.001
Number of Events	1249	2065	
Exposure Time (Subject-Month)	3040.8	3375.5	
Event Rate	0.41	0.61	0.0027
Severe Hypoglycemia			
Number of subjects at risk	323	331	
Number of subjects with events (%)[b]	14 (4.33)	33 (9.97)	0.0066
Number of events	22	74	
Exposure time (subject-months)	3040.8	3375.5	
Event rate (per 100 subject-months)	0.72	2.19	0.0591
Glucose ≤ 49 mg/dL or Reversed Symptom Event Rates [c]			
Number of subjects at risk	323	331	
Number of subjects with events (%)[b]	96 (29.72)	138 (41.69)	0.0015
Number of events	351	607	
Exposure time (subject-months)	3040.8	3375.5	
Event rate (per 100 subject-months)	0.12	0.18	0.0419

a: p-value is from GEE analysis comparing total hypoglycemia event rates between TI and BPR 70/30 (premixed insulin) based on Poisson distribution with the terms treatment and time period (3 months) in the model. “Pooled sites” was also a term in the analysis for any hypoglycemia.

b: Percentage is calculated based on the total number of subjects at risk.

c: Criterion included hypoglycemia with plasma glucose ≤49 mg/dL or, in the absence of a plasma glucose measurement, clinical symptoms that were reversed by oral carbohydrate, subcutaneous glucagon, or intravenous glucose administration.

8.3.2.3 Serious TEAEs of Hypoglycemia in T2DM Subjects

Table 28 summarizes serious TEAEs of hypoglycemia in T2DM subjects in the pooled Phase 2/3 trial 2013 Resubmission Safety Population. The incidence rates and types of serious TEAEs related to hypoglycemia were similar between TI and active comparator groups. In Trial 175, SAEs related to hypoglycemia were reported by 1 subject in the TI group. In Trial 102, SAEs related to hypoglycemia were reported in 4/323 (1.2%) subjects in the TI group and 6/331 (1.8%) subjects in the BPR 70/30 arm.

Table 28: Serious TEAEs of Hypoglycemia in T2DM Subjects (2013 Resubmission Safety Population)

System Organ Class Preferred Term	TI [N=1991] SYE=1356 n (%)	TP [N=290] SYE=98 n (%)	Comparator [N=1363] SYE=1374 n (%)
Metabolism and nutrition disorders	12 (0.6)	0 (0.0)	18 (1.3)
Hypoglycaemia	8 (0.4)	0 (0.0)	9 (0.7)
Nervous system disorders	14 (0.7)	1 (0.3)	14 (1.0)
Hypoglycaemic coma	0 (0.0)	0 (0.0)	1 (0.1)
Hypoglycaemic seizure	1 (0.1)	0 (0.0)	0 (0.0)
Loss of consciousness	4 (0.2)	0 (0.0)	3 (0.2)

Notes:

Each subject was counted only once per system organ class and preferred term combined.
Percentages were based on the number of subjects in each treatment group in the Safety Population.
SAEs designated as "loss of consciousness" or "hypoglycemic unconsciousness" were associated with severe hypoglycemia.

8.4 Patient Report Outcomes

Quality-of-life data was collected using a validated survey tool. Throughout Trial 171, health-related quality-of-life data was measured with the EuroQol (EQ)-5D, a standardized instrument that measures health-related quality of life across five dimensions (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression) and the EQ VAS (a 20-cm vertical visual analogue scale [VAS]) that generates a self-rating of health-related quality of life.[41] Data was collected at baseline, Visit 8, and Visit 10 (end of study). An optimal health state is assigned a score of 100. The health utility score provides a simple descriptive profile and a single index value for health status and can be used in the clinical and economic evaluation of health care as well as in population health surveys. In Trial 171, respondents' self-rated measure of health using the VAS showed a greater improvement in the TI Gen2 group than in the comparator (insulin aspart) group. The between-group difference was 2.6 (SD 1.12; 95% CI, 0.4 to 4.8) in favor of the TI Gen2 group. Additionally, from baseline to Week 24, both treatment groups had stable assessments of the 5 dimensions of health (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression). Although insulin treatment has been associated with a reduction in health utility scores, the improvement in the quality of life reported in both treatment groups could be related to the inherent improvement in glycemic control associated with insulin use which has been shown to be positively associated with a high level of perceived quality of life. Furthermore, the small but greater improvement in the quality of life reported by the TI Gen2 group could be associated with the convenience of dosing (ease of use) and a reduction in stigmatization experienced by the TI Gen2 group.

An ITQ was used in Trial 171 to probe subject experience with the Gen2 inhaler. Subjects rated their experience with the Gen2 inhaler positively; 88% of all answers were "agree" or "strongly agree." Attitudes and perceptions of the Gen2 inhaler remained positive and did not change over the course of 24 weeks of use.

Fear of Hypoglycemia Survey data were also collected in Trial 171. The Fear of Hypoglycemia Survey includes a Behavior domain and a Worry domain. A slight reduction in hypoglycemia-avoiding behaviors (survey points) was seen in both the TI Gen2 and insulin aspart groups with no clinically relevant difference between the groups. A slight decrease in Worry (survey points) was seen in the TI Gen2 group and a slight increase (survey points) was seen in the insulin aspart group; however, the 95% CI for the between-group difference included zero.

8.5 Dosing Recommendations

Dosing instructions for TI are provided in Appendix 7.

TI cartridges can be described in terms of fill content or delivered content. TI cartridges are discussed in terms of fill content (10 U and 20 U Gen2 cartridges and 15 U and 30 U MedTone cartridges) throughout most of this document. However, in the dosing instructions (Appendix 7), TI cartridge units are discussed in terms of the delivered insulin in units equivalent to sc insulin ("3U" and "6U" Gen2 cartridges). The lower dose Gen2 cartridge has a 10 U fill and delivers the equivalent of 3 units of sc insulin. The higher dose Gen2 cartridge has a 20 U fill and delivers the equivalent of 6 units of sc insulin. Thus, in the prescribing information, the conversion factor for converting the smallest possible dose of TI to sc insulin is 3.

Over the course of TI development, the conversion factor has evolved. The clinical studies submitted in the 2009 Original NDA, including Phase 3 Trial 009 (T1DM) and Trial 102 (T2DM) assumed a bioavailability of about 30%, (ie, one 15 U MedTone cartridge approximated 5 units sc insulin) as a conservative approach to initiating TI therapy to ensure subject safety and avoid potential insulin overdose during the transition from injected insulin to TI. Based on the MedTone dosing data from these earlier trials, the recently completed Phase 3 Trial 171 (T1DM) and Trial 175 (T2DM) used a conversion factor in which the 10 U Gen2 cartridge or the 15 U Medtone cartridge was assumed to approximate 4 units of sc insulin.

The final conversion factor (used in the dosing instructions) is derived from the new trials conducted with TI Gen2 including PK data (Trials 176 and 177) and clinical data (Trials 171 and 175). In Trial 171, the overall mean daily prandial insulin dose was 102.7 U for the TI group and 25.5 units for the insulin aspart treatment group resulting in an aspart/TI dose ratio of 25%. Recent PK trials suggest a bioavailability of approximately 30% for TI compared with sc RAA or sc RHI. Based upon the results of Trial 171 (that utilized a conversion factor of 10 U TI approximating 4 units sc RHI or RAA) and the most recent BA data, a 3-unit conversion factor is proposed for use in the prescribing information. Patients will be informed that the 10 U cartridge approximates 3 units of sc injected insulin (and is labeled as "3 units").

8.6 Efficacy Conclusions

The efficacy of TI in improving glycemic control in subjects with diabetes, both T1DM and T2DM, especially as it compares with current standard of care therapies, has been clearly

demonstrated in the TI clinical program. TI was noninferior to active comparators in 2 of 3 trials (Trials 171 in T1DM and 102 in T2DM, but not Trial 009 in T1DM) and superior to placebo (Trial 175 in T2DM) in HbA1c reduction as demonstrated in 24 to 52-week clinical trials. The glycemic lowering effect was durable as noted in the trials with 52-week treatment duration. More subjects attained target HbA1c goals with TI than with placebo. On the whole, the proportion of subjects attaining HbA1c goals with TI was not different from that observed with insulin comparators, although more subjects treated with RAA insulin aspart achieved HbA1c ≤ 7.0% in Trial 171. A greater decrease in FPG in the TI plus basal insulin group compared with the comparator insulin plus basal insulin group has been a consistent finding. In T1DM subjects, TI use was associated with mild weight loss. In T2DM subjects, TI use was associated with modest weight gain compared to placebo, but it was less than noted with comparator insulin over a 52-week period.

A lower incidence and/or event rate of hypoglycemia was noted in trials in insulin-using diabetic subjects, both T1DM and T2DM. For severe hypoglycemia event rates, TI was associated with clinically meaningful reductions from comparator rates. More hypoglycemia was noted compared to placebo in insulin-naïve T2DM subjects. When analyzed by background OAD use, the event rate of all hypoglycemic events in TI-treated subjects on metformin was not different than the event rate in placebo-treated subjects on metformin and SU, a very commonly used therapeutic two-drug combination therapy.

9 CLINICAL SAFETY

The TI development program provides a comprehensive safety assessment of the TI Inhalation System in T1DM and T2DM populations. New data since the submission of the 2009 Original NDA and the 2010 Amendment have shown no significant changes in the TI safety profile. TI administered with the Gen2 inhaler has the same safety and tolerability profile as TI administered with the MedTone Inhaler. TI continues to be well-tolerated for the control of hyperglycemia in adult subjects with T1DM or T2DM.

Key safety conclusions are listed below:

- Total exposure to trial treatment:
  - TI: 3017 subjects (2052 subject-years of exposure)
  - Active comparator: 2198 subjects (2152 subject-years of exposure)
  - Technosphere particles (placebo): 290 subjects (98 subject-years of exposure)
- Incidence and severity of all causality TEAEs, excluding cough, were similar between the TI and comparator groups. Cough, reported more frequently with TI, was generally mild, dry, transient, occurred within 10 minutes of inhalation of the dry powder, and diminished with time. The incidence rates and characteristics of the cough were similar for the 2 inhaler types.
- The incidences of SAEs were similar between TI and comparator groups. The incidence of SAEs related to hypoglycemia, the most common treatment-related SAE, was 1.6% for TI group and 2.2% for comparator group. In the 2013 Resubmission Safety Population, 10 (0.3%) TI-treated subjects and 7 (0.3%) comparator-treated subjects died. An additional 6 deaths in uncontrolled/compassionate use trials occurred through the data cutoff date of 31 Jul 2013.

- More subjects who received TI than comparator discontinued treatment early due to TEAEs, primarily those affecting the respiratory tract. This imbalance was primarily due to cough.
- A small decrease in FEV_1 was noted within the first 3 months of initiating therapy in clinical trials. This decrease was greater (treatment group difference, 42 mL at Month 3) in subjects treated with TI versus comparator. After the first 3 months, the annual rate of decline was comparable in both treatment groups. The difference in FEV_1 between the 2 treatment groups was no longer seen by 4 weeks after discontinuation of TI. A direct comparison of lung function, pulmonary safety data, device-related AEs, and device performance in subjects treated with TI administered using either the Gen2 or MedTone inhalers revealed no difference between the safety profiles of the inhalers.
- A long-term safety and efficacy trial in patients with asthma and COPD is ongoing. Limited data are available regarding the use of TI in subjects with underlying lung disease. In a clinical pharmacology study, 5 of 17 subjects with asthma developed bronchoconstriction, wheezing, and/or asthma exacerbation upon receiving TI; two of these events were considered SAEs necessitating subject discontinuation from the trial (Trial 113). Symptoms were relieved promptly with bronchodilators. In subjects with COPD in a Phase 1 trial (Trial 015), serial spirometry showed an approximately 9% (range 3% to 15%) mean acute decline of FEV_1 after a single dose of TI. Based on the available safety data, proposed labeling will contraindicate TI use in people with asthma, COPD, or other chronic lung disease.
- No CV safety signal was noted with the use of TI.
- In the 2013 Resubmission Safety Population, the incidence of overall malignancies reported by TI subjects was 0.43% compared with 0.32% reported by comparator-treated subjects with no predominance of any specific type of cancer or clustering by organ system. Observed incidence of malignancies did not exceed the rate that would be expected in the general US population (SEER, 2000-2010).[42]
- Two patients treated with TI, one in a controlled clinical trial, and one in an uncontrolled extension trial developed lung cancer. This observed lung cancer incidence of 0.8 cases per 1,000 person-years in subjects treated with TI in clinical trials does not exceed the rate that would be expected among individuals (nonsmokers and smokers) with diabetes (1 to 2 cases per 1,000 person-years).
- As expected, there was an increased insulin antibody response to TI relative to comparator insulin. This was more pronounced in T1DM subjects, was not associated with any clinical consequences, and decreased towards baseline several months after discontinuing therapy.
- There were no safety signals for TI treatment and potentially immunogenic events, ophthalmic events, laboratory abnormalities, vital sign measurements, and ECGs. Two long-term trials suggested an imbalance of DKA events in T1DM subjects. Most of these events were related to concurrent infection and treatment interruption and/or reduced dosing. With reinforced investigative site education, no additional cases have been noted since the 2009 Original NDA.
- In general, TI was well tolerated in both T1DM and T2DM subjects.

9.1 Overview

The clinical safety data based on adverse event (AE) reporting is presented for the primary population supporting safety, the 2013 Resubmission Safety Population, which consists of all subjects who had at least 1 dose of trial drug in controlled Phase 2 and Phase 3 trials, with >14 days of planned continuous trial drug treatment regardless of device. This included 13 pooled controlled Phase 2/3 clinical trials with 3017 patients exposed to TI, 290 patients exposed to TP, and 2198 patients exposed to comparator treatments. The trials and the pooling strategy are presented in Section 7.3.

For the 2013 Resubmission Safety Population, the extent of exposure to trial drug, demography, and baseline characteristics, and disposition of the trial populations are presented followed by a summary of treatment-emergent AEs (TEAEs) structured as follows:

- Overview of TEAEs,
- TEAEs experienced by ≥2% of subjects,
- Deaths (also includes non-pooled trials and compassionate use program),
- Serious AEs (SAEs),
- TEAEs leading discontinuation,
- Safety in clinical pharmacology trials.

The following special safety topics are discussed in more detail:

- Pulmonary safety,
- Cardiovascular safety,
- Neoplasms,
- Anti-insulin antibodies,
- Adverse events of special interest (including diabetic ketoacidosis [DKA], potential immunogenic events, and AEs of the eye).

Lastly, other safety evaluations (laboratory results other than glucose, vital signs, and ECGs), and safety in subpopulations and ongoing trials will be presented.

Clinical safety is presented for 3 trial populations: subjects receiving TI, TP, or active comparator, unless otherwise specified. The TI groups for T1DM, T2DM, and combined T1DM and T2DM are not distinguished by type of inhaler used (MedTone versus Gen2) because the head-to-head pulmonary safety comparison (Trial 171) showed the 2 inhalers to have similar safety profiles (Section 4.4 and Section 9.5). However, in the presentations of extent of exposure and pulmonary safety, some or all results are presented by inhaler type.

9.2 Extent of Exposure

TI has been studied in approximately 6500 adult diabetic subjects and healthy volunteers in clinical development program. Of these, 5505 were subjects with T1DM or T2DM who participated in the Phase 2/3 clinical trials with duration of exposure of > 14 days and were included in the 2013 Resubmission Safety Population. Trial treatment exposure is summarized in Table 29 and Table 30.

Overall exposure is as follows:

- 3017 subjects (2052 subject-years of exposure [SYE]) were exposed to TI (2647 subjects [1903 SYE] via MedTone inhaler and 370 [149 SYE] via Gen2 inhaler);
- 290 subjects (98 SYE) were exposed to TP;
- 2198 subjects (2152 SYE) were exposed to comparator treatments.

In addition, 229 patients with T2DM participated in an uncontrolled extension study (Trial 010) and were followed for up to 4 years (199 subjects [86.9%] were exposed to TI for >12 months, 175 subjects [76.4%] were exposed for up to 24 months). A total of 60 subjects (26.2%) were exposed for more than 36 months and 31 subjects (13.5%) were exposed between 42 and 48 months.

Table 29: Number (Percentage) of Subjects Exposed to Treatment for Defined Durations by Treatment and Inhaler (2013 Resubmission Safety Population T1DM and T2DM Combined)

Exposure Duration	TI Total			TP Total			Comparator
	Gen2 (N=370)	MedTone (N=2647)	Total (N=3017)	Gen2 (N=176)	MedTone (N=114)	Total (N=290)	Total (N=2198)
Overall	370 (100.0)	2647 (100.0)	3017 (100.0)	176 (100.0)	114 (100.0)	290 (100.0)	2198 (100.0)
0-3 months	56 (15.1)	840 (31.7)	896 (29.7)	23 (13.1)	62 (54.4)	85 (29.3)	314 (14.3)
>3-6 months	297 (80.3)	681 (25.7)	978 (32.4)	150 (85.2)	52 (45.6)	202 (69.7)	560 (25.5)
>6-12 months	17 (4.6)	402 (15.2)	419 (13.9)	3 (1.7)	0	3 (1.0)	392 (17.8)
>12-24 months	0	718 (27.1)	718 (23.8)	0	0	0	913 (41.5)

Abbreviations: TI=Technosphere Insulin; TP=Technosphere particles (placebo, no insulin).

Table 30: Subject-Years of Exposure by Type of Diabetes, Number of Subjects, and Treatment for the 2013 Resubmission Safety Population

Type of Diabetes	TI Total		TP Total		Comparator	
	N	SYE	N	SYE	N	SYE
Type 1 Diabetes	1026	697	-	-	835	778
Type 2 Diabetes	1991	1356	290	98	1363	1374
Combined Type 1 and Type 2 Diabetes	3017	2052[a]	290	98	2198	2152

Abbreviations: SYE=subject-years of exposure; TI=Technosphere Insulin; TP=Technosphere particles (placebo, no insulin).
a: The combined SYE (2052) is not exactly Type 1 diabetes (697) plus Type 2 diabetes (1356) due to rounding of all 3 SYE numbers.

9.3 Demography, Baseline Characteristics, and Disposition

Demographic and baseline characteristics for the 2013 Resubmission Safety Population are shown in Table 31. Within the T1DM and T2DM populations in the 2013 Resubmission Safety Population, the treatment groups were well balanced with respect to gender (approximately 50% each), race (mostly Caucasian), smoking history, and mean age, weight, body mass index (BMI). Subjects in the T1DM population were younger, had a lower BMI,

and had a longer mean duration of diabetes and a lower proportion of smokers compared with subjects in the T2DM population.

Table 31: Demographic and Baseline Characteristics by Diabetes Type and Treatment (2013 Resubmission Safety Population)

Characteristics	T1DM		T2DM		
	TI Total [N=1026]	Comparator [N=835]	TI Total [N=1991]	TP Total [N=290]	Comparator [N=1363]
Age (years)					
Mean (SD)	38.5 (12.64)	38.7 (12.47)	56.3 (8.75)	56.4 (9.02)	55.8 (8.82)
Range	(18,76)	(18,76)	(19,82)	(26,79)	(18,78)
Sex, n(%)					
Male	518 (50.5)	427 (51.1)	1014 (50.9)	139 (47.9)	696 (51.1)
Female	508 (49.5)	408 (48.9)	977 (49.1)	151 (52.1)	667 (48.9)
Race, n(%)					
Caucasian	907 (88.4)	754 (90.3)	1584 (79.6)	207 (71.4)	1090 (80.0)
Black	38 (3.7)	23 (2.8)	111 (5.6)	18 (6.2)	65 (4.8)
Hispanic	66 (6.4)	49 (5.9)	227 (11.4)	55 (19.0)	144 (10.6)
Asian	9 (0.9)	3 (0.4)	44 (2.2)	7 (2.4)	38 (2.8)
Other	6 (0.6)	6 (0.7)	25 (1.3)	3 (1.0)	26 (1.9)
Weight (kg)					
Mean (SD)	76.4 (15.27)	75.7 (14.93)	88.4 (17.06)	90.5 (16.31)	88.0 (17.54)
Range	(42,132)	(42,136)	(48,180)	(56,137)	(47,170)
BMI (kg/m²)					
Mean (SD)	26.0 (4.10)	25.8 (3.98)	31.2 (4.80)	31.8 (4.63)	31.0 (4.83)
Range	(16.0,39.6)	(0.3,41.4)	(15.3,55.6)	(21.0,44.4)	(19.2,64.4)
Duration of Diabetes (years)					
Mean (SD)	16.6 (10.97)	16.7 (10.62)	10.7 (6.61)	8.8 (5.02)	11.5 (7.20)
Past History of Smoking					
Yes	221 (21.5)	187 (22.4)	594 (29.8)	84 (29.0)	403 (29.6)

Abbreviations: BMI=body mass index; SD=standard deviation; TI=Technosphere Insulin; TP=Technosphere particles (placebo, no insulin).

Subject disposition for the 2013 Resubmission Safety Population is summarized in Table 32. More subjects prematurely discontinued the trial in the TI groups than in the comparator groups, with the most common reasons for discontinuation being subject withdrawal of consent and AEs. Subject and Investigator comments were reviewed for subjects withdrawing consent to determine if there was an associated safety concern. If a subject had comments suggesting that a safety-related cause may have contributed to discontinuation, the case was further reviewed. Adverse events that led to discontinuation are presented in Section 9.4.4; in general, the imbalance noted for TI treatment groups in both T1DM and T2DM versus comparator groups was due to respiratory events (most frequently cough). It is possible that the higher rate of withdrawal was related to the lack of experience with this new insulin product; for patients treated with comparator insulin products, withdrawal may have

been less attractive since they were receiving the standard-of-care treatment with which they were quite familiar, and upon discontinuation would have fewer treatment options. Open-label design may have influenced these results as well. When TI was compared with TP in double-blind Trial 175, the incidences of TEAEs resulting in trial discontinuation were similar: 4.0% in the TI group and 5.1% in the TP (placebo) group.

Table 32: Subject Disposition by Diabetes Type and Treatment (2013 Resubmission Safety Population)

Disposition	T1DM		T2DM		
	TI Total n (%)	Comparator n (%)	TI Total n (%)	TP Total n (%)	Comparator n (%)
Safety Population	1026 (100)	835 (100)	1991 (100)	290 (100)	1363 (100)
Completed Trial Treatment	692 (67.4)	687 (82.3)	1331 (66.9)	232 (80.0)	1028 (75.4)
Prematurely Discontinued	334 (32.6)	148 (17.7)	660 (33.1)	58 (20.0)	335 (24.6)
Adverse Events Including Laboratory Abnormality	72 (7.0)	3[a] (0.4)	149 (7.5)	11 (3.8)	24 (1.8)
Protocol Violation	17 (1.7)	19 (2.3)	38 (1.9)	5 (1.7)	13 (1.0)
Subject Withdrew Consent	170 (16.6)	67 (8.0)	264 (13.3)	25 (8.6)	175 (12.8)
Subject Died	1 (0.1)	2 (0.2)	7[b] (0.4)	0	4[c] (0.3)
Investigator Decision	28 (2.7)	8 (1.0)	43 (2.2)	2 (0.7)	16 (1.2)
Lost to Follow-Up	19 (1.9)	33 (4.0)	60 (3.0)	4 (1.4)	83 (6.1)
Other	26 (2.5)	16 (1.9)	99 (5.0)	11 (3.8)	20 (1.5)
Unknown	1 (0.1)	0	0	0	0

a: An additional subject died after a head injury in a car accident (2 fatal events); however, on the trial summary case report form, the reason for discontinuation was recorded as death rather than an adverse event.
b: Two additional subjects died during the follow-up period.
c: An additional subject died during the follow-up period (not a premature discontinuation of treatment).

9.4 Treatment-Emergent Adverse Events

A brief overview of TEAEs for the 2013 Resubmission Safety Population is presented in Table 33. The incidence of SAEs was similar for TI and comparator groups. For the T1DM and T2DM populations combined, the percentages of subjects with at least 1 TEAE were similar for the TI and comparator groups; this was also the case for severe TEAEs. Higher percentages of subjects in the TI groups discontinued due to TEAEs.

Table 33: Brief Summary of Treatment Emergent Adverse Events (2013 Resubmission Safety Population)

Parameter	T1DM		T2DM			T1DM and T2DM Combined	
	TI Total [N=1026] [SYE=697] n (%)	**Comparator [N=835] [SYE=778] n (%)**	**TI Total [N=1991] [SYE=1356] n (%)**	**TP Total [N=290] [SYE=98] n (%)**	**Comparator [N=1363] [SYE=1374] n (%)**	**Total [N=3017] [SYE=2052] n (%)**	**Comparator [N=2198] [SYE=2152] n (%)**
Any TEAE	698 (68.0)	523 (62.6)	1260 (63.3)	153 (52.8)	814 (59.7)	1958 (64.9)	1337 (60.8)
Fatal TEAE	1 (0.1)	2 (0.2)	8[a] (0.4)	0	2[b] (0.1)	9[a] (0.3)	4[b] (0.2)
SAE (excluding death)	93 (9.1)	83 (9.9)	120 (6.0)	11 (3.8)	106 (7.8)	213 (7.1)	189 (8.6)
TEAE Leading to Discontinuation	68 (6.6)	4 (0.5)	149 (7.5)	10 (3.4)	20 (1.5)	217 (7.2)	24 (1.1)
Severe TEAE	107 (10.4)	87 (10.4)	130 (6.5)	16 (5.5)	94 (6.9)	237 (7.9)	181 (8.2)

Abbreviations: SYE=subject-year of exposure.
a: One additional subject in the T2DM TI group died (see Table 35, neuroendocrine tumor) during the 30-day follow-up period.
b: Three additional subjects in the T2DM comparator group died (see Table 35). Their eventually-fatal TEAEs occurred during the trials, but their deaths due to these TEAEs occurred in the follow-up period.

9.4.1 Common Treatment-Emergent Adverse Events

Excluding cough, the overall TEAE profiles for TI and comparator groups were similar based on TEAEs experienced by at least 2% of the subjects in any treatment group in the combined T1DM and T2DM population (Table 34); corresponding tables for the separated T1DM population and the T2DM population are in Appendix 8. For both, cough and upper respiratory tract infection were the most frequently reported TEAEs. Cough and, to a lesser extent, oropharyngeal pain and throat irritation were noted to be associated with inhalation of the TI dry powder, which is not surprising. Cough and other respiratory events are presented by inhaler device and further discussed in Section 9.5.5.

Table 34. T1DM and T2DM Combined: All Causality Treatment-emergent Adverse Events (Incidence ≥2%) (2013 Resubmission Safety Population)

Preferred Term	TI Total [N=3017] SYE=2052 n (%)	TP Total [N=290] SYE=98 n (%)	Comparator [N=2198] SYE=2152 n (%)
Any TEAE	1958 (64.9)	153 (52.8)	1337 (60.8)
Cough	811 (26.9)	57 (19.7)	114 (5.2)
Upper respiratory tract infection	284 (9.4)	14 (4.8)	239 (10.9)
Nasopharyngitis	220 (7.3)	24 (8.3)	172 (7.8)
Headache	109 (3.6)	8 (2.8)	47 (2.1)
Influenza	110 (3.6)	3 (1.0)	99 (4.5)
Bronchitis	90 (3.0)	10 (3.4)	58 (2.6)
Oropharyngeal pain	77 (2.6)	8 (2.8)	25 (1.1)
Hypertension	75 (2.5)	3 (1.0)	70 (3.2)
Diarrhoea	71 (2.4)	4 (1.4)	45 (2.0)
Throat irritation	68 (2.3)	4 (1.4)	3 (0.1)
Urinary tract infection	62 (2.1)	2 (0.7)	53 (2.4)
Productive cough	57 (1.9)	3 (1.0)	18 (0.8)
Sinusitis	55 (1.8)	3 (1.0)	49 (2.2)
Hypoglycaemia	50 (1.7)	0	51 (2.3)
Back pain	48 (1.6)	5 (1.7)	43 (2.0)

Note(s): Adverse events were coded using the MedDRA dictionary (Version 15.1).
Each subject is counted only once per system organ class and preferred term combined.
Percentages are based on the number of subjects in each treatment group in the Safety Population.

9.4.2 Deaths

As of 31 July 2013, a total of 23 deaths have been reported in the entire TI clinical development program (Table 35). None of the deaths were considered to be related to any trial treatment. Sixteen of the subjects who died were exposed to TI (10 in controlled trials and 6 in uncontrolled trials [including compassionate use]) and 7 were exposed to comparator. In 9 of the 10 subjects who died in the TI group, death was due to TEAEs during the controlled trials; the other subject discontinued study treatment due to a TEAE and then died during the 30-day follow-up period.

For the controlled trials, using the 2013 Resubmission Safety Population as the denominator, 10 (0.33%) of 3017 TI subjects and 7 (0.32%) of 2198 comparator subjects died. The exposure-adjusted death rates were 0.44 per 100 subject-years and 0.33 per 100 subject-years for the TI and comparator groups, respectively.

Table 35: Deaths in the Entire TI Clinical Development Program Including All Controlled and Uncontrolled Trials

Subject Number	Diabetes	Cause of Death
TI in Controlled Phase 2/3 Trials		
MKC-TI-030/3469	Type 1	Circulatory collapse
MKC-TI-030/3254[a]	Type 2	Bile duct cancer (after discontinuation of treatment)
MKC-TI-030/0539	Type 2	Ischemic stroke and acute myocardial infarction
MKC-TI-102/2524	Type 2	Hemorrhagic stroke
MKC-TI-030/0237	Type 2	Cardiac arrest
MKC-TI-030/0611	Type 2	Aortic valve stenosis, cardiomegaly, a nuclear cataract and diabetic retinal edema, cerebral infarct, cerebrovascular accident, coma, hydrocephalus, supranuclear palsy, atelectasis, intracardiac thrombus, mitral valve incompetence, tricuspid valve incompetence, cardiac murmur, atherosclerosis, hypertension, pulmonary hypertension, cardiac arrest, and respiratory failure
MKC-TI-102/2158	Type 2	Worsened pre-existing ischemic heart disease
MKC-TI-102/2219	Type 2	Acute myocardial infarction, pulmonary edema, and hypertensive cardiopathy
MKC-TI-102/2891	Type 2	Staphylococcal sepsis, cardiac failure, duodenal ulcer hemorrhage, gangrene, diabetes mellitus inadequate control, and pneumonia
MKC-TI-102/2909[a]	Type 2	Neuroendocrine tumor involving lungs
TI in Uncontrolled Trials		
MKC-TI-005/1854	Type 2	Acute myocardial infarction
MKC-TI-005/3316	Type 2	Bronchial carcinoma
MKC-TI-005/0246	Type 2	Prostate cancer metastatic
PDC-INS-0008/2782	Type 2	Pancreatic carcinoma metastatic
MKC-TI-139/011	Type 2	Complications of leukemia

Table 35: Deaths in the Entire TI Clinical Development Program Including All Controlled and Uncontrolled Trials

Subject Number	Diabetes	Cause of Death
TI in Named Patient/Compassionate Use Program		
MK201000002 Compassionate Use Program Switzerland	Type 1	Died while asleep. History of previous MI. Investigator felt CVD was the likely cause of death.
Comparator in Controlled Trials		
MKC-TI-030/1783 (usual care)	Type 1	Road traffic accident with associated head injury
MKC-TI-030/3282 (usual care)	Type 2	Cardiac arrest
MKC-TI-030/0308 (usual care)	Type 2	Cerebrovascular accident
MKC-TI-102/1772 (bi-phasic rapid-acting insulin 70/30)	Type 2	Cardiac arrest
MKC-TI-014/678 (insulin aspart)	Type 2	Acute coronary syndrome
MKC-TI-171/1413 (insulin aspart/insulin detemir)	Type 1	Accidental drowning
Comparator Off Treatment		
MKC-TI-014/074	Type 2	Acute cardiac coronary failure

a: Died during the 30-day follow-up period.

9.4.3 Serious Adverse Events

The incidences of SAEs, excluding deaths, were similar between TI and comparator treatments in subjects with either T1DM or T2DM (Table 36). The most frequent SAEs were metabolism and nutrition disorders for subjects with T1DM, and cardiac disorders for subjects with T2DM. Hypoglycemia was the most common SAE in both the TI and comparator groups in the combined T1DM and T2DM population. Hypoglycemia is further discussed in Section 8.3.

Table 36: Serious Adverse Events (SAEs), Excluding Deaths, by SOC and PT ≥0.2% in T1DM and T2DM (2013 Resubmission Safety Population)

	T1DM		T2DM		
System Organ Class	TI Total [N=1026] [SYE=697] n (%)	Comparator [N=835] [SYE=778] n (%)	TI Total [N=1991] [SYE=1356] n (%)	TP Total [N=290] [SYE=98] n (%)	Comparator [N=1363] [SYE=1374] n (%)
Any Serious TEAE	93 (9.1)	83 (9.9)	120 (6.0)	11 (3.8)	106 (7.8)
Cardiac Disorders	4 (0.4)	6 (0.7)	25 (1.3)	3 (1.0)	23 (1.7)
Coronary artery disease	1 (0.1)	0	5 (0.3)	1 (0.3)	3 (0.2)
Myocardial infarction	1 (0.1)	1 (0.1)	5 (0.3)	0	3 (0.2)
Atrial fibrillation	0	0	3 (0.2)	0	3 (0.2)
Angina pectoris	0	1 (0.1)	0	1 (0.3)	2 (0.1)
Angina unstable	1 (0.1)	0	1 (0.1)	0	3 (0.2)
Cyanosis	0	0	0	1 (0.3)	0

Table 36: Serious Adverse Events (SAEs), Excluding Deaths, by SOC and PT ≥0.2% in T1DM and T2DM (2013 Resubmission Safety Population)

System Organ Class	T1DM		T2DM		
	TI Total [N=1026] [SYE=697] n (%)	Comparator [N=835] [SYE=778] n (%)	TI Total [N=1991] [SYE=1356] n (%)	TP Total [N=290] [SYE=98] n (%)	Comparator [N=1363] [SYE=1374] n (%)
Congenital, Familial and Genetic Disorders	0	0	0	1 (0.3)	0
Skull malformation	0	0	0	1 (0.3)	0
Eye Disorders	0	1 (0.1)	5 (0.3)	0	2 (0.1)
Retinal detachment	0	0	3 (0.2)	0	0
Gastrointestinal Disorders	4 (0.4)	7 (0.8)	11 (0.6)	1 (0.3)	7 (0.5)
Gastrooesophageal reflux disease	0	2 (0.2)	0	0	0
Pancreatitis acute	1 (0.1)	0	3 (0.2)	0	0
Inguinal hernia, obstructive	0	0	0	1 (0.3)	0
General Disorders and Administration Site Conditions	1 (0.1)	0	5 (0.3)	0	3 (0.2)
Hepatobiliary Disorders	4 (0.4)	2 (0.2)	5 (0.3)	0	5 (0.4)
Cholecystitis	0	1 (0.1)	3 (0.2)	0	3 (0.2)
Cholelithiasis	2 (0.2)	0	3 (0.2)	0	3 (0.2)
Infections and Infestations	3 (0.3)	10 (1.2)	26 (1.3)	0	19 (1.4)
Urinary tract infection	0	0	3 (0.2)	0	1 (0.1)
Pneumonia	0	1 (0.1)	2 (0.1)	0	4 (0.3)
Cellulitis	0	1 (0.1)	1 (0.1)	0	3 (0.2)
Appendicitis	1 (0.1)	1 (0.1)	0	0	4 (0.3)
Injury, Poisoning and Procedural Complications	9 (0.9)	9 (1.1)	9 (0.5)	1 (0.3)	10 (0.7)
Ankle fracture	1 (0.1)	3 (0.4)	0	0	0
Road traffic accident	1 (0.1)	2 (0.2)	1 (0.1)	0	2 (0.1)
Fall	0	0	1 (0.1)	0	5 (0.4)
Humerus fracture	0	0	0	1 (0.3)	0
Investigations	0	1 (0.1)	1 (0.1)	1 (0.3)	0
Heart rate decreased	0	0	0	1 (0.3)	0
Metabolism and Nutrition Disorders	56 (5.5)	47 (5.6)	12 (0.6)	1 (0.3)	18 (1.3)
Hypoglycaemia	41 (4.0)	40 (4.8)	8 (0.4)	0	9 (0.7)
Diabetic ketoacidosis	10 (1.0)	3 (0.4)	0	0	1 (0.1)
Ketoacidosis	3 (0.3)	0	1 (0.1)	0	1 (0.1)
Hyperglycaemia	2 (0.2)	1 (0.1)	2 (0.1)	0	1 (0.1)
Diabetes mellitus inadequate control	1 (0.1)	2 (0.2)	1 (0.1)	0	4 (0.3)

Table 36: Serious Adverse Events (SAEs), Excluding Deaths, by SOC and PT ≥0.2% in T1DM and T2DM (2013 Resubmission Safety Population)

System Organ Class	T1DM		T2DM		
	TI Total [N=1026] [SYE=697] n (%)	Comparator [N=835] [SYE=778] n (%)	TI Total [N=1991] [SYE=1356] n (%)	TP Total [N=290] [SYE=98] n (%)	Comparator [N=1363] [SYE=1374] n (%)
Musculoskeletal and Connective Tissue Disorders	2 (0.2)	3 (0.4)	12 (0.6)	2 (0.7)	9 (0.7)
Rotator cuff syndrome	2 (0.2)	0	0	0	0
Intervertebral disc protrusion	0	2 (0.2)	2 (0.1)	0	1 (0.1)
Back pain	0	0	1 (0.1)	1 (0.3)	2 (0.1)
Neoplasms Benign, Malignant and Unspecified (Including Cysts & Polyps)	2 (0.2)	1 (0.1)	12 (0.6)	1 (0.3)	9 (0.7)
Nervous System Disorders	22 (2.1)	15 (1.8)	14 (0.7)	1 (0.3)	14 (1.0)
Loss of consciousness	9 (0.9)	6 (0.7)	4 (0.2)	0	3 (0.2)
Hypoglycaemic unconsciousness	7 (0.7)	4 (0.5)	0	0	0
Hypoglycaemic seizure	5 (0.5)	6 (0.7)	1 (0.1)	0	0
Cerebrovascular accident	0	0	0	0	5 (0.4)
Ischaemic stroke	0	0	0	1 (0.3)	1 (0.1)
Psychiatric Disorders	0	3 (0.4)	2 (0.1)	0	0
Suicide attempt	0	2 (0.2)	0	0	0
Renal and Urinary Disorders	0	0	4 (0.2)	0	6 (0.4)
Nephrolithiasis			1 (0.1)	0	3 (0.2)
Reproductive System and Breast Disorders	2 (0.2)	0	2 (0.1)	0	2 (0.1)
Respiratory, Thoracic and Mediastinal Disorders	3 (0.3)	0	5 (0.3)	0	2 (0.1)
Skin and Subcutaneous Tissue Disorders	0	0	2 (0.1)	2 (0.7)	2 (0.1)
Hyperhidrosis	0	0	1 (0.1)	1 (0.3)	0
Vascular Disorders	0	1 (0.1)	6 (0.3)	0	3 (0.2)

Abbreviations: MedDRA=Medical Dictionary for Regulatory Activities; PT=preferred term; SAEs=serious adverse events; SOC=system organ class; SYE=subject-year exposure; TIDM=type 1 diabetes mellitus; T2DM=type 2 diabetes mellitus; TI=Technosphere Insulin.
Note: Adverse events were coded using the MedDRA dictionary (Version 15.1). This table includes only SAEs that are treatment-emergent.

9.4.4 Treatment-Emergent Adverse Events Leading to Discontinuation

The percentages of subjects who had TEAEs that led to discontinuation were higher in the TI groups in the T1DM (6.6%) and T2DM (7.5%) populations relative to active comparator (0.5% for T1DM and 1.5% for T2DM) or placebo (3.4% for T2DM) groups (Table 37). Respiratory TEAEs were the most common events that led to permanent early discontinuation in subjects using TI. These TEAEs were primarily cough and dyspnea with incidences of 3.3% and 0.6%, respectively, in subjects with T1DM and 2.5% and 0.5%, respectively, in subjects with T2DM.

Table 37: TEAEs by SOC and PT ≥0.2% That Led to Permanent Early Discontinuation (2013 Resubmission Safety Population)

	T1DM		T2DM		
System Organ Class Preferred Term	**TI Total [N=1026] [SYE=697] n (%)**	**Comparator [N=835] [SYE=778] n (%)**	**TI Total [N=1991] [SYE=1356] n (%)**	**TP Total [N=290] [SYE=98] n (%)**	**Comparator [N=1363] [SYE=1374] n (%)**
Any TEAE	68 (6.6)	4 (0.5)	149 (7.5)	10 (3.4)	20 (1.5)
Blood and Lymphatic System Disorders	0	0	1 (0.1)	0	2 (0.1)
Cardiac Disorders	3 (0.3)	0	15 (0.8)	0	4 (0.3)
Myocardial infarction	0	0	3 (0.2)	0	1 (0.1)
Myocardial ischaemia	0	0	3 (0.2)	0	0
Eye Disorders	2 (0.2)	0	1 (0.1)	0	1 (0.1)
Gastrointestinal Disorders	3 (0.3)	0	5 (0.3)	1 (0.3)	0
Dry mouth	1 (0.1)	0	0	1 (0.3)	0
General Disorders and Administration Site Conditions	4 (0.4)	0	11 (0.6)	1 (0.3)	0
Chest discomfort	1 (0.1)	0	4 (0.2)	1 (0.3)	0
Immune System Disorders	1 (0.1)	0	3 (0.2)	1 (0.3)	0
Drug hypersensitivity	1 (0.1)	0	1 (0.1)	1 (0.3)	0
Infections and Infestations	3 (0.3)	1 (0.1)	14 (0.7)	0	1 (0.1)
Injury, Poisoning and Procedural Complications	0	1 (0.1)	1 (0.1)	0	3 (0.2)
Investigations	3 (0.3)	0	5 (0.3)	0	0
Metabolism and Nutrition Disorders	8 (0.8)	1 (0.1)	14 (0.7)	0	6 (0.4)
Hyperglycaemia	3 (0.3)	0	10 (0.5)	0	1 (0.1)
Hypoglycaemia	3 (0.3)	0	0	0	4 (0.3)
Diabetes mellitus inadequate control	2 (0.2)	0	2 (0.1)	0	0
Musculoskeletal and Connective Tissue Disorders	1 (0.1)	0	2 (0.1)	0	1 (0.1)
Neoplasms Benign, Malignant and Unspecified (Including Cysts And Polyps)	1 (0.1)	0	5 (0.3)	1 (0.3)	1 (0.1)
Nervous System Disorders	5 (0.5)	0	14 (0.7)	1 (0.3)	3 (0.2)
Headache	2 (0.2)	0	4 (0.2)	0	0
Ischaemic stroke	0	0	1 (0.1)	1 (0.3)	0

Table 37: TEAEs by SOC and PT ≥0.2% That Led to Permanent Early Discontinuation (2013 Resubmission Safety Population)

System Organ Class Preferred Term	T1DM		T2DM		
	TI Total [N=1026] [SYE=697] n (%)	Comparator [N=835] [SYE=778] n (%)	TI Total [N=1991] [SYE=1356] n (%)	TP Total [N=290] [SYE=98] n (%)	Comparator [N=1363] [SYE=1374] n (%)
Pregnancy, Puerperium and Perinatal Conditions	0	1 (0.1)	0	0	0
Psychiatric Disorders	1 (0.1)	0	2 (0.1)	0	1 (0.1)
Respiratory, Thoracic and Mediastinal Disorders	45 (4.4)	0	79 (4.0)	7 (2.4)	1 (0.1)
Cough	34 (3.3)	0	49 (2.5)	6 (2.1)	0
Dyspnoea	6 (0.6)	0	9 (0.5)	0	0
Bronchial obstruction	2 (0.2)	0	0	0	0
Wheezing	0	0	2 (0.1)	1 (0.3)	0
Nasal congestion	0	0	0	1 (0.3)	0
Skin and Subcutaneous Tissue Disorders	0	0	3 (0.2)	0	0
Surgical and Medical Procedures	0	0	1 (0.1)	0	0
Vascular Disorders	2 (0.2)	0	1 (0.1)	0	2 (0.1)

Abbreviations: PT=preferred term; SOC=system organ class; SYE=subject-year exposure.

9.4.5 Non-Pooled Clinical Pharmacology Trials

Overall, TI and TP were well tolerated in the clinical pharmacology trials. No clinically meaningful safety events occurred that were unique to the clinical pharmacology trials. There were no SAEs or deaths in these trials. The most commonly reported TEAEs were cough and hypoglycemia.

9.5 Pulmonary Safety

Pulmonary safety of TI was evaluated extensively in the clinical development program through an assessment of both TEAEs and pulmonary function tests (PFTs) because of the nature of the drug (inhaled route of administration) and the transition from the MedTone to the Gen2 inhaler. A head-to-head comparison of the 2 inhalers was performed to bridge the more recent TI Gen2 pulmonary safety data with the extensive TI MedTone pulmonary safety database. In this direct comparison as well as across the different submissions (2009 Original NDA, 2010 Amendment, and 2013 Resubmission), pulmonary safety findings were similar and consistent regarding overall incidence and type of respiratory TEAEs (including the incidence and characteristics of cough or serious respiratory TEAEs) for the 2 inhalers. The pulmonary safety section is organized as follows:

- Overview of the pulmonary safety program
  - Respiratory TEAE data collection and trial pooling/reporting strategy
  - PFT data collection and trial pooling/reporting strategy
- Respiratory TEAEs – common, serious, and leading to discontinuation of trial treatment
- Cough

- PFT data
  - Pooled Trials
  - Trial 171
  - Trial 175
- Subjects with underlying lung disease
  - Diagnosed asthma and chronic obstructive pulmonary disease (COPD)

9.5.1 Overview of the Pulmonary Safety Program

All subjects participated in a comprehensive pulmonary safety program that was rigorously conducted and monitored. The pulmonary clinical safety assessments were based on TEAE reporting, including cough details collected on a specific cough case report form (CRF). Protocol-mandated PFTs were obtained at frequent, specified intervals in all trials (see Appendix 9 for protocol-specified testing schedules); the PFT analyses are based on nearly 34,000 tests.

In addition, chest X-rays were obtained at baseline and at the end of the treatment period for trials of shorter duration or annually in trials of >1 year duration.

High resolution computed tomography (HRCT) or magnetic resonance imaging (MRI) was obtained as part of the pulmonary safety program in 472 subjects (4 clinical trials). Chest HRCTs (or MRIs in Germany) were obtained in all subjects who participated in the 2 controlled Phase 2 trials (Trial 005 and Trial PDC-INS-0008). Images were obtained at baseline and at the end of the 12-week treatment period. After completion of these 2 trials, subjects were invited to participate in uncontrolled extension Trial 010 in which they received chest HRCT (or MRI in Germany) annually. In addition, subsets of subjects with T1DM or T2DM who participated in 2-year pulmonary safety Trial 030 in US sites were randomly assigned to undergo annual chest HRCTs.

All HRCT images were reviewed centrally by independent, board-certified radiologists. During the reviews, the radiologist was blinded to subject identity, investigator site, examination dates, sequence of examinations, and reason for the imaging (scheduled or unscheduled). All available images for a given subject were reviewed during a single session. All images for subjects with HRCT findings considered other than “normal” by the independent radiologist underwent secondary, joint review by an independent, board-certified radiologist who was different from the primary reviewer and a board-certified pulmonologist. The secondary reviewers were supplied with the clinical data including medical history, adverse events, laboratory and PFT results, and concomitant medications, but were blinded to the clinical trial treatment group. Based on review of all the clinical and radiological data, the secondary reviewers determined whether the images were “normal,” “abnormal, not clinically significant,” or “abnormal, clinically significant,” and provided a final interpretation in a subject narrative.

9.5.2 Pulmonary Function Testing Program

9.5.2.1 Collection of Pulmonary Function Test Data

The PFT program was rigorously conducted and monitored, and strict adherence by investigative sites to American Thoracic Society and/or European Respiratory Society (ATS/ERS) recommendations was required. PFTs for trials that started before July 2005 were conducted under 1994 ATS recommendations, and PFTs for trials that started on or after July 2005 were conducted under the 2005 joint ATS/ERS Task Force recommendations. All PFTs were performed only at MKC-certified pulmonary function laboratories (PFLs). Certification of the PFLs was based on successful completion of the initial on-site equipment verification, extensive hands-on training by qualified personnel, and submission of a minimum of 10 acceptable biologic control tests that met the 2005 ATS/ERS pulmonary test performance and quality standards. After the PFL was certified, each PFL entered into an ongoing quality control program to ensure continued reliability of testing. All pulmonary function tests performed by trial subjects were submitted for central, blinded review by independent Registered Pulmonary Function Technologists credentialed by the National Board for Respiratory Care and specifically trained on the 2005 ATS/ERS test quality and reporting recommendations and the MKC PFT program. Tests that did not meet ATS/ERS performance criteria for acceptability or repeatability were to be repeated within 7 days of notification. PFT assessments included spirometry (FVC and FEV_1), body plethysmography to measure total lung capacity (TLC), and lung diffusion capacity for carbon monoxide (DL_{CO}).

A pre-specified "PFT finding" of a ≥15% decrease from baseline in FVC, FEV_1, TLC, or DL_{CO} was defined in the Phase 3 protocols for safety monitoring and to assist the investigators in noting changes from baseline requiring determination of clinical significance. The 15% threshold took into account the expected inherent variability associated with technical and biological factors in such measurements.

Earlier Phase 2/3 trial PFT assessment included body plethysmography and spirometry; more recently, in Trials 171 and 175, with FDA agreement, only spirometry testing was performed at PFLs. Thus, only spirometry results are presented in this document.

9.5.2.2 Key Pulmonary Inclusion/Exclusion Criteria

Key pulmonary exclusion criteria for the Phase 2/3 trials included having active respiratory disease, a history of asthma or chronic obstructive pulmonary disease (COPD), and current smoking or urine cotinine level >100 ng/dL. Former smokers who stopped smoking at least 6 months before screening were allowed. Subjects could not have had clinically significant radiological findings on screening chest x-ray. Key PFT eligibility criteria were as follows:

- FEV_1 ≥70% Third National Health and Nutrition Examination Survey (NHANES III) predicted
- FVC ≥70% NHANES III predicted
- FEV_1/FVC ≥ NHANES III lower limit of normal (LLN)

9.5.2.3 Analysis of Pulmonary Function Tests

For the pooled data, MMRM was conducted to evaluate the overall adjusted treatment differences in PFTs. The following factors were fitted in the model: disease type (for combined population), age, height, gender, baseline PFT, time (visit), treatment, and region. Adjusted (least-square [LS]) estimates of the mean and LS mean differences with 95% CIs were calculated for each time point. Estimates of annual rate of change (slope) in PFT parameters were calculated using a random coefficient analysis. The model included treatment, disease type, region, baseline pulmonary function data, age, height, gender, and time (in years). The treatment group difference (TI – comparator group) in the annual rate of change and corresponding 2-sided 95% CI were calculated using a random coefficient model. Missing data were not imputed.

9.5.3 Pooling Strategy

Pulmonary safety data were pooled using 2 strategies. For respiratory TEAEs, cough, and chest x-rays, data were pooled (similar to what was done for general safety) from controlled Phase2/3 trials with continuous exposure to trial treatment for more than 14 days (2013 Resubmission Safety Population). The respiratory TEAEs, including cough as an adverse event of special interest, are presented for the 2013 Resubmission Safety Population as described in Section 7.3. PFT data from controlled trials with treatment durations of at least 12 months were pooled. Thus, Trials 009 and 030 (T1DM subjects) were pooled for T1DM and Trials 102 and 030 (T2DM subjects) were pooled for T2DM; for simplicity, this document refers to this pooled population as the pooled PFT population. PFT data from the completed new trials in the 2013 Resubmission are reported by trial rather than pooled because of shorter treatment duration:

- Trial 171, T1DM, open-label, 24-week treatment period with a head-to-head comparison of the 2 inhalers;
- Trial 175, T2DM, double-blind, 24-week treatment period in which the comparator was inhaled TP rather than a non-inhaled treatment;

Data from nonpooled trials in subjects with asthma and/or COPD are presented trial-by-trial.

9.5.4 Overall Respiratory TEAEs

The incidence of respiratory TEAEs was higher in the TI group (45.2%) than in either the TP (35.9%) or comparator (31.0%) groups (Table 38). This difference was predominantly due to cough being reported by 26.9% of subjects in the TI group compared with 19.7% in the TP and 5.2% in the comparator groups. Cough, an anticipated side effect of inhalation of a dry powder formulation, was pre-specified as an expected event of special interest and is further discussed in Section 9.5.5. Dyspnea was uncommon, reported by 1.4% of subjects in the TI group, 0.7% in the TP group, and 0.3% in the comparator group. Most TEAEs of dyspnea were mild or moderate in severity, non-serious, and quickly resolved without any specific treatment. Other respiratory TEAEs of interest (asthma, wheezing, bronchospasm, bronchial hyperreactivity) were uncommon with incidence rates <1.0% in TI subjects. The overall

incidence of respiratory TEAEs in subjects who received TI was similar between the TI MedTone group (45.5%) and the TI Gen2 group (42.7%). This was also true for cough (26.8% in TI MedTone and 27.3% in TI Gen2).

Table 38: Respiratory TEAEs Experienced by ≥2% Subjects in Any Group for the Combined T1DM and T2DM Population by Treatment and Inhaler (2013 Resubmission Safety Population)

	TI			TP			
Preferred Term	Gen2 [N=370] [SYE=149] n (%)	MedTone [N=2647] [SYE=1903] n (%)	Total [N=3017] [SYE=2052] n (%)	Gen2 [N=176] [SYE=73] n (%)	MedTone [N=114] [SYE=25] n (%)	Total [N=290] [SYE=98] n (%)	Comparator [N=2198] [SYE=2152] n (%)
Any TEAE	158 (42.7)	1205 (45.5)	1363 (45.2)	60 (34.1)	44 (38.6)	104 (35.9)	682 (31.0)
Cough	101 (27.3)	710 (26.8)	811 (26.9)	36 (20.5)	21 (18.4)	57 (19.7)	114 (5.2)
URI	27 (7.3)	257 (9.7)	284 (9.4)	5 (2.8)	9 (7.9)	14 (4.8)	239 (10.9)
Nasopharyngitis	20 (5.4)	200 (7.6)	220 (7.3)	8 (4.5)	16 (14.0)	24 (8.3)	172 (7.8)
Bronchitis	11 (3.0)	79 (3.0)	90 (3.0)	7 (4.0)	3 (2.6)	10 (3.4)	58 (2.6)
Oropharyngeal pain	11 (3.0)	66 (2.5)	77 (2.6)	4 (2.3)	4 (3.5)	8 (2.8)	25 (1.1)
Throat irritation	9 (2.4)	59 (2.2)	68 (2.3)	2 (1.1)	2 (1.8)	4 (1.4)	3 (0.1)
Productive cough	1 (0.3)	56 (2.1)	57 (1.9)	0	3 (2.6)	3 (1.0)	18 (0.8)
Sinusitis	5 (1.4)	50 (1.9)	55 (1.8)	2 (1.1)	1 (0.9)	3 (1.0)	49 (2.2)
Dyspnoea	8 (2.2)	33 (1.2)	41 (1.4)	2 (1.1)	0	2 (0.7)	6 (0.3)
Respiratory tract infection viral	5 (1.4)	4 (0.2)	9 (0.3)	5 (2.8)	0	5 (1.7)	5 (0.2)

Abbreviations: SYE=subject-year exposure; URI=upper respiratory (tract) infection.

Note: Adverse events were coded using the MedDRA dictionary (Version 15.1).

The overall incidence of respiratory SAEs was low across treatment groups for the combined T1DM and T2DM population: 0.4% in the total TI group with no clinically significant difference between inhaler types (0.3% in TI Gen2 and 0.4% in TI MedTone), 0% in the TP group, and 0.4% in the comparator group (Table 39). The most common respiratory SAE was pneumonia reported in 0.1% of subjects in the TI group and 0.2% of subjects in the comparator group. Other respiratory SAEs occurred in no more than 1 subject per treatment group (TI or comparator).

Table 39: Respiratory Serious Adverse Events (SAEs) >0.1% for the Combined T1DM and T2DM Population by Treatment and Inhaler (2013 Resubmission Safety Population)

System Organ Class Preferred Term	TI			TP			Comparator [N=2198] [SYE=2152] n (%)
	Gen2 [N=370] [SYE=149] n (%)	MedTone [N=2647] [SYE=1903] n (%)	Total [N=3017] [SYE=2052] n (%)	Gen2 [N=176] [SYE=73] n (%)	MedTone [N=114] [SYE=25] n (%)	Total [N=290] [SYE=98] n (%)	
Any TEAE	1 (0.3)	11 (0.4)	12 (0.4)	0	0	0	9 (0.4)
Pneumonia	0	2 (0.1)	2 (0.1)	0	0	0	5 (0.2)
Bronchitis	0	0	0	0	0	0	1 (0.0)
Bronchial hyperreactivity	1 (0.3)	0	1 (0.0)	0	0	0	0

Abbreviations: SYE=subject-year exposure.
Note(s):
Each SOC includes the total number of subjects by SOC.
Within an SOC, a subject may be counted more than once in different preferred terms.

The overall incidence of respiratory TEAEs leading to discontinuation of trial treatment was similar for most of the inhaled treatments (TI Total [4.6%], TI Gen2 [4.9%], TI MedTone [4.5%], and TP Total [2.4%], TP Gen2 [4.0%], TP MedTone [0.0%]), and this incidence was higher than for the non-inhaled comparator (0.1%). Cough (2.8%) and dyspnea (0.5%) were the most common TEAEs leading to discontinuation for TI-treated subjects regardless of inhaler (Table 40).

Table 40: Respiratory TEAEs ≥0.1% Resulting in Trial Discontinuation for the Combined T1DM and T2DM Population by Treatment and Inhaler (2013 Resubmission Safety Population)

System Organ Class/Preferred Term	TI			TP			Comparator [N=2198] [SYE=2152] n (%)
	Gen2 [N=370] [SYE=149] n (%)	MedTone [N=2647] [SYE=1903] n (%)	Total [N=3017] [SYE=2052] n (%)	Gen2 [N=176] [SYE=73] n (%)	MedTone [N=114] [SYE=25] n (%)	Total [N=290] [SYE=98] n (%)	
ANY TEAE	18 (4.9)	120 (4.5)	138 (4.6)	7 (4.0)	0	7 (2.4)	3 (0.1)
INFECTIONS AND INFESTATIONS	0	15 (0.6)	15 (0.5)	0	0	0	2 (0.1)
Bronchitis	0	6 (0.2)	6 (0.2)	0	0	0	0
Upper respiratory tract infection	0	4 (0.2)	4 (0.1)	0	0	0	0
Pneumonia	0	2 (0.1)	2 (0.1)	0	0	0	1 (0.0)
Pulmonary tuberculosis	0	1 (0.0)	1 (0.0)	0	0	0	1 (0.0)
INVESTIGATIONS	0	3 (0.1)	3 (0.1)	0	0	0	0
Pulmonary function test decreased	0	2 (0.1)	2 (0.1)	0	0	0	0
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	18 (4.9)	106 (4.0)	124 (4.1)	7 (4.0)	0	7 (2.4)	1 (0.0)
Cough	12 (3.2)	71 (2.7)	83 (2.8)	6 (3.4)	0	6 (2.1)	0
Dyspnoea	5 (1.4)	10 (0.4)	15 (0.5)	0	0	0	0
Asthma	0	4 (0.2)	4 (0.1)	0	0	0	0
Throat irritation	0	4 (0.2)	4 (0.1)	0	0	0	0
Bronchial hyperreactivity	1 (0.3)	2 (0.1)	3 (0.1)	0	0	0	0
Bronchial obstruction	0	2 (0.1)	2 (0.1)	0	0	0	0
Bronchospasm	0	2 (0.1)	2 (0.1)	0	0	0	0
Oropharyngeal pain	1 (0.3)	1 (0.0)	2 (0.1)	0	0	0	0
Respiratory tract congestion	0	2 (0.1)	2 (0.1)	0	0	0	0
Wheezing	0	2 (0.1)	2 (0.1)	1 (0.6)	0	1 (0.3)	0
Dyspnoea exertional	1 (0.3)	0	1 (0.0)	0	0	0	0
Nasal congestion	0	0	0	1 (0.6)	0	1 (0.3)	0

Abbreviations: SYE=subject-year exposure.
Note(s):
Each SOC includes the total number of subjects by SOC.
Within an SOC, a subject may be counted more than once in different preferred terms.

9.5.5 Cough

Cough was further analyzed from data collected on a specific cough case report form (CRF) that collected information about cough events including frequency of cough (single defined, intermittent, continuous), relationship to treatment, and presence of sputum. In cases of mild cough, the event may not have been recorded as an adverse event; thus, the total number of cough events (from the cough CRF) may be different from the total number of coughs reported as TEAEs (from the adverse event CRF).

As summarized in Table 41, cough was reported by a higher percentage of subjects in the TI (26.3%) and TP (20.3%) groups than in the comparator group (5.1%). Regardless of the inhaler, cough was predominantly mild, dry, intermittent, or a single defined event and not considered serious. Cough occurred shortly after inhalation of TI or TP. The percentage of subjects with new onset of cough was highest during the first week of treatment and then declined rapidly over the next 12 weeks (Figure 27). The excess incidence of cough declined to approximately 2% by the third month of treatment. Similarly, the TI cough event rate was also highest during the first week after initiation of treatment (0.52 events/subject-month), and declined to 0.23 events/subject-month (Week 2) and 0.09 events/subject-month (Week 3), and remained <0.07 events/subject-month over the subsequent 24 months.

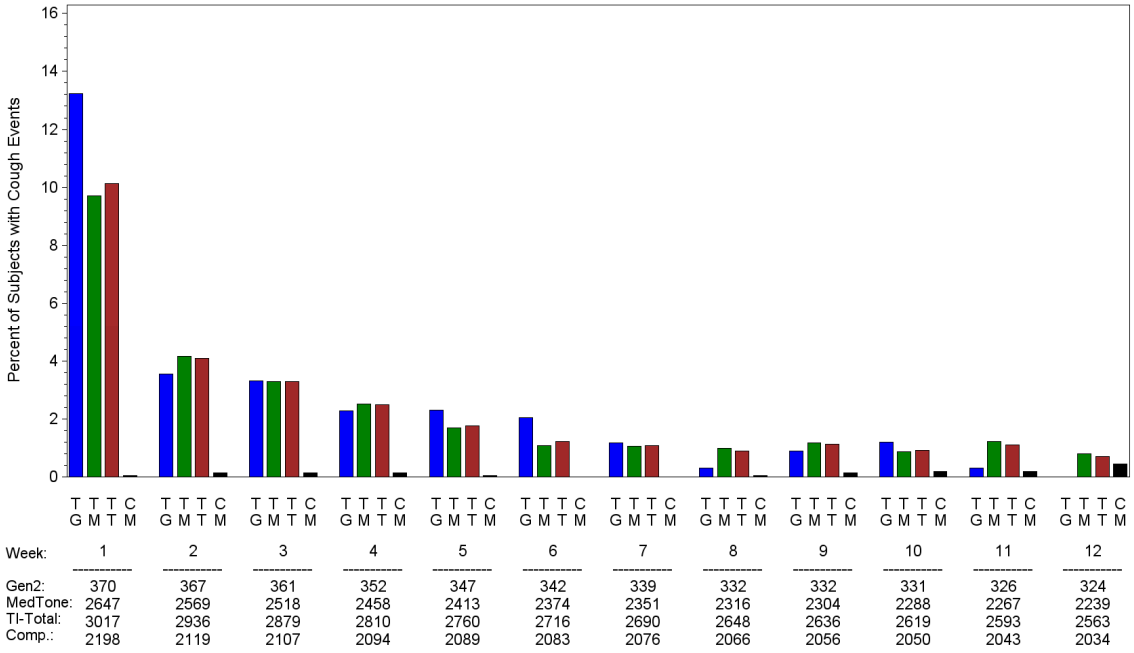
Except for the first week of therapy, the percentages of subjects experiencing cough were comparable between TI Gen2 and TI MedTone groups. Cough leading to discontinuation was noted in 2.8% of the TI patients. No meaningful differences were noted in changes in lung function in patients who reported cough and those who did not. Overall pattern and characteristics of cough were similar regardless of the inhaler used to administer TI.

Table 41: Incidence and Characteristics of Cough as a TEAE of Special Interest in T1DM and T2DM Combined (2013 Resubmission Safety Population)

	TI Gen2 [N=370] n (%)	TI MedTone [N=2647] n (%)	TI Total [N=3017] n (%)	TP Gen2 [N=176] n (%)	TP MedTone [N=114] n (%)	TP Total [N=290] n (%)	Comparator [N=2198] n (%)
Number of Subjects Reporting Cough [1]	101 (27.3)	691 (26.1)	792 (26.3)	36 (20.5)	23 (20.2)	59 (20.3)	112 (5.1)
Number of Total Cough Episodes	124	1340	1464	44	124	168	131
Frequency of Coughing [2]							
Continuous	9 (7.3)	82 (6.1)	91 (6.2)	6 (13.6)	5 (4.0)	11 (6.5)	10 (7.6)
Intermittent	88 (71.0)	749 (55.9)	837 (57.2)	30 (68.2)	93 (75.0)	123 (73.2)	99 (75.6)
Single Defined	27 (21.8)	509 (38.0)	536 (36.6)	8 (18.2)	26 (21.0)	34 (20.2)	21 (16.0)
Cough Occurred within 10 minutes of Drug Administration[2]							
Yes	110 (88.7)	1015 (75.7)	1125 (76.8)	38 (86.4)	101 (81.5)	139 (82.7)	16 (12.2)
No	14 (11.3)	322 (24.0)	336 (23.0)	6 (13.6)	23 (18.5)	29 (17.3)	83 (63.4)
Was the cough Sputum producing [2]?							
Yes	18 (14.5)	186 (13.9)	204 (13.9)	7 (15.9)	4 (3.2)	11 (6.5)	26 (19.8)
No	106 (85.5)	620 (46.3)	726 (49.6)	37 (84.1)	19 (15.3)	56 (33.3)	79 (60.3)
Cough Related to [2]							
Spirometry	0	6 (0.4)	6 (0.4)	0	3 (2.4)	3 (1.8)	0
Trial Drug	0	558 (41.6)	558 (38.1)	0	107 (86.3)	107 (63.7)	0
Other	0	156 (11.6)	156 (10.7)	0	10 (8.1)	10 (6.0)	40 (30.5)

[1] Percentages are based on the number of subjects in each treatment group from the Safety Population.
[2] Percentages are based on the total number of cough episodes in each treatment group. The 'No' category might include events that happened while the subject was temporarily not on treatment.
Note: Only data from the cough CRF is presented in this table.

Figure 27: Percentage of Subjects Experiencing Coughs versus Time Since Initiation of Trial Drug by Treatment and Inhaler (2013 Resubmission Safety Population T1DM and T2DM Combined)



Week:	1	2	3	4	5	6	7	8	9	10	11	12
Gen2:	370	367	361	352	347	342	339	332	332	331	326	324
MedTone:	2647	2569	2518	2458	2413	2374	2351	2316	2304	2288	2267	2239
TI-Total:	3017	2936	2879	2810	2760	2716	2690	2648	2636	2619	2593	2563
Comp.:	2198	2119	2107	2094	2089	2083	2076	2066	2056	2050	2043	2034

Abbreviations: TG=TI Gen2; TM=TI MedTone; TT=TI Total; CM=comparator

9.5.6 Pulmonary Function Testing

PFT results are presented for the pooled PFT population with T1DM and T2DM subjects combined and for Trial 171 (TIDM) and Trial 175 (T2DM) as individual trials. In the pooled PFT population (described in Section 9.5.3), the pattern and magnitude of changes in lung function were similar between subjects with T1DM or T2DM; thus, the results are presented with T1DM and T2DM combined.

9.5.6.1 Pooled Trials

BASELINE PFT VALUES

Mean values and percentage predicted for FEV_1, FVC, and FEV_1/FVC were similar between the TI and comparator groups at baseline (Table 42).

Table 42: Baseline PFT Values, Absolute and Percentage Predicted, T1DM and T2DM (Pooled PFT Population)

PFT Parameter	T1DM		T2DM		T1DM and T2DM Combined	
	TI (N=556)	Comparator (N=540)	TI (N=976)	Comparator (N=1002)	TI (N=1532)	Comparator (N=1542)
	Mean ± SD (% predicted)	Mean ± SD (% predicted)	Mean ± SD (% predicted)	Mean ± SD (% predicted)	Mean ± SD (% predicted)	Mean ± SD (% predicted)
FEV_1 (L)	3.51 ± 0.770 (96.42)	3.54 ± 0.809 (96.81)	3.02 ± 0.699 (96.37)	3.04 ± 0.746 (96.60)	3.20 ± 0.762 (96.39)	3.21 ± 0.806 (96.67)
FVC (L)	4.41 ± 0.991 (98.0)	4.44 ± 1.005 (98.24)	3.87 ± 0.910 (95.43)	3.89 ± 0.980 (95.85)	4.07 ± 0.975 (96.36)	4.08 ± 1.022 (96.69)
FEV_1/FVC (%)	79.87 ± 6.322 (98.32)	80.05 ± 6.349 (98.45)	78.40 ± 5.47 (100.7)	78.34 ± 5.53 (100.5)	78.93 ± 5.836 (99.81)	78.94 ± 5.885 (99.79)

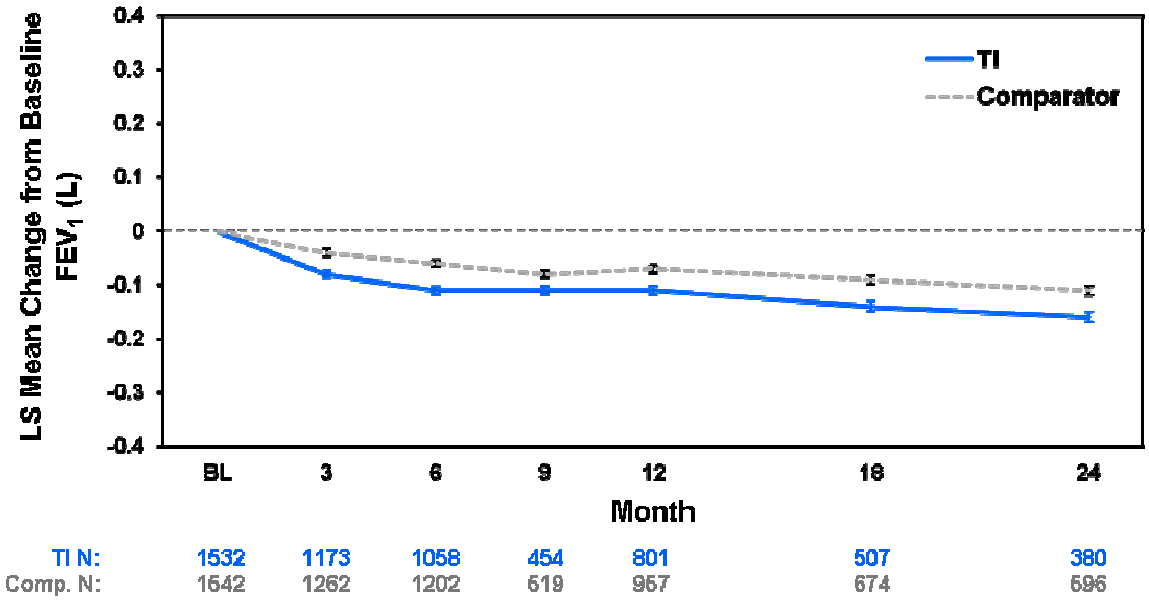
Abbreviations: FEV_1=forced expiratory volume in 1 second; FVC=forced vital capacity; PFT=pulmonary function test.
Trials contributing to the pooled PFT population: MKC-TI-009, MKC-TI-030, and MKC-TI-102.

EFFECTS ON PULMONARY FUNCTION (FEV_1 RESULTS)

In the pooled PFT population, subjects in both the TI and comparator groups showed small declines from baseline in mean FEV_1 at each time point (Months 3, 6, 9, 12, 18, and 24) with a greater initial decline for subjects in the TI group (Figure 28; Appendix 10). After the initial declines for both groups, FEV_1 remained fairly constant. The difference in FEV_1 between the treatment groups remained unchanged through the last assessment time point at Month 24. The LS mean difference (TI minus comparator) in the change from baseline in FEV_1 was −0.040 L at 3 months, −0.043 L at 6 months, −0.036 L at 9 months, −0.038 L at 12 months, −0.045 L at 18 months, and −0.045 L at 24 months. These data suggest that the effect of TI on FEV_1 is small and non-progressive over 24 months of continued treatment.

FVC results for the pooled PFT population were consistent with FEV_1 results.

Figure 28: LS Mean (SE) Change from Baseline in FEV_1 (Liters) by Visit using the MMRM Model for the Pooled Combined T1DM and T2DM PFT Population



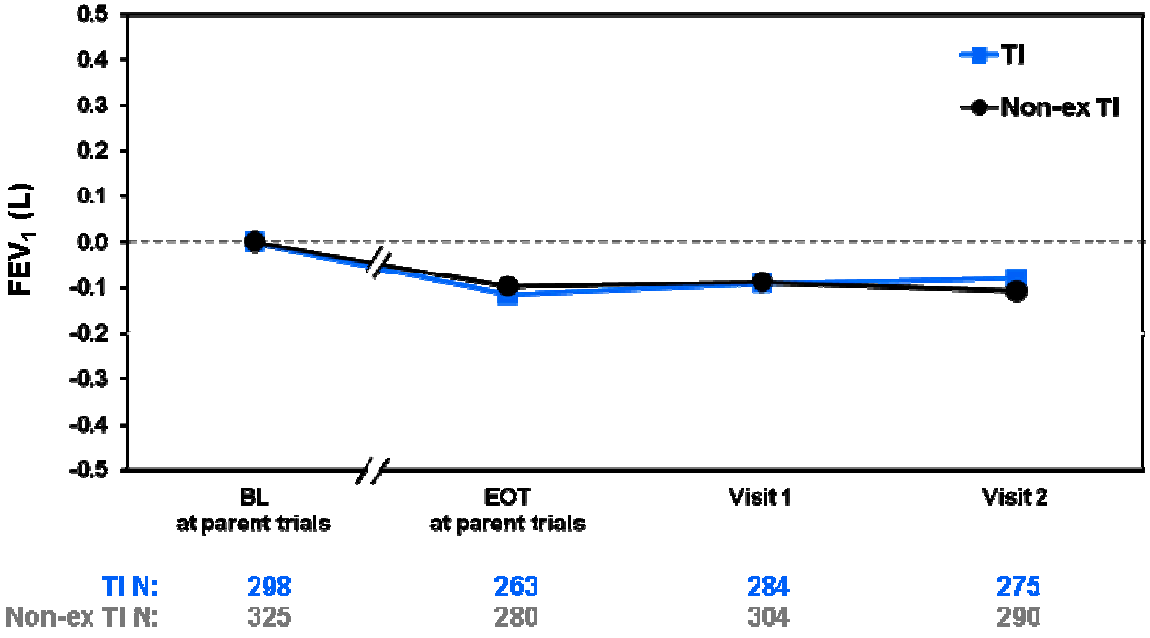
Abbreviations: FEV_1=forced expiratory volume in 1 second; LS Mean=least square mean; TI N=number of subjects on TI treatment; Comp. N=number of subjects on comparator treatment; SE=standard error.

Trials contributing to the pooled PFT population: MKC-TI-009, MKC-TI-030, and MKC-TI-102.

CHANGES IN PULMONARY FUNCTIONS AFTER CESSATION OF TI (TRIAL 126)

To better define the reversibility of the decline in FEV_1, Trial 126 was conducted as a pulmonary follow-up trial for T1DM and T2DM subjects who completed participation in any one of the following trials with treatment durations ranging from 6 months to 2 years: Trials 009, 102, 103, and 030. Of 649 patients, 315 (121 with T1DM, 194 with T2DM) received TI and 334 (129 with T1DM, 205 with T2DM) received comparator during the parent trials. Baseline characteristics were similar between the TI and non-TI groups for age, gender, and type and duration of diabetes. After completion of the parent trial, all subjects resumed their usual anti-diabetic regimen, and PFTs were done at the certified PFT labs at 1 month and 3 months after the final TI treatment of the parent trial irrespective of the duration of exposure and type of diabetes. As can be seen in Figure 29, the difference in FEV_1 between treatment groups disappeared within 1 month of TI discontinuation. Thus, the lung function changes associated with TI in subjects with T1DM or T2DM are small, non-progressive, and resolve after discontinuation of TI.

Figure 29: Mean (SE) Change from Parent-Trial Baseline in FEV_1 by Visit in Extension Trial 126 (Safety Population)



Abbreviations: EOT=end of treatment; FEV_1=forced expiratory volume in one second; TI N=number of "ex TI" subjects who were treated with TI in the parent trial; Non-ex TI N=number of "non-ex TI" subjects who were treated with something other than TI in the parent trial; SE=standard error; TI=Technosphere Insulin.

To further clarify the effects of long-term therapy with TI, the annual rate of change (slope) in FEV_1 from Month 3 (first assessment after Baseline) to Month 24 (final assessment) was estimated for each treatment group in the pooled PFT population (Table 43). There was no statistical difference in the annual rate of change in FEV_1 between the treatment groups.

Table 43: Annual Rate of Change in FEV_1 (Liters) Between Month 3 and Month 24 for the Pooled Combined T1DM and T2DM PFT Population

	TI (N=1225)	Comparator (N=1356)	TI- Comparator
LS Mean	-0.047	-0.040	-0.0070
SE	0.0048	0.0042	0.0063
95% CI	(-0.057, -0.038)	(-0.048, -0.032)	(-0.019, 0.005)

Abbreviations: CI=confidence interval; FEV_1=forced expiratory volume in 1 second; LS Mean=least square mean; SE=standard error.

Trials contributing to the pooled PFT population: MKC-TI-009, MKC-TI-030, and MKC-TI-102.

POTENTIAL IMPACT OF EARLY DROPOUTS

In the large, 2-year pulmonary safety trial (Trial 030), similar to pooled safety population, the most frequent reason for early discontinuation in both the TI and comparator groups was

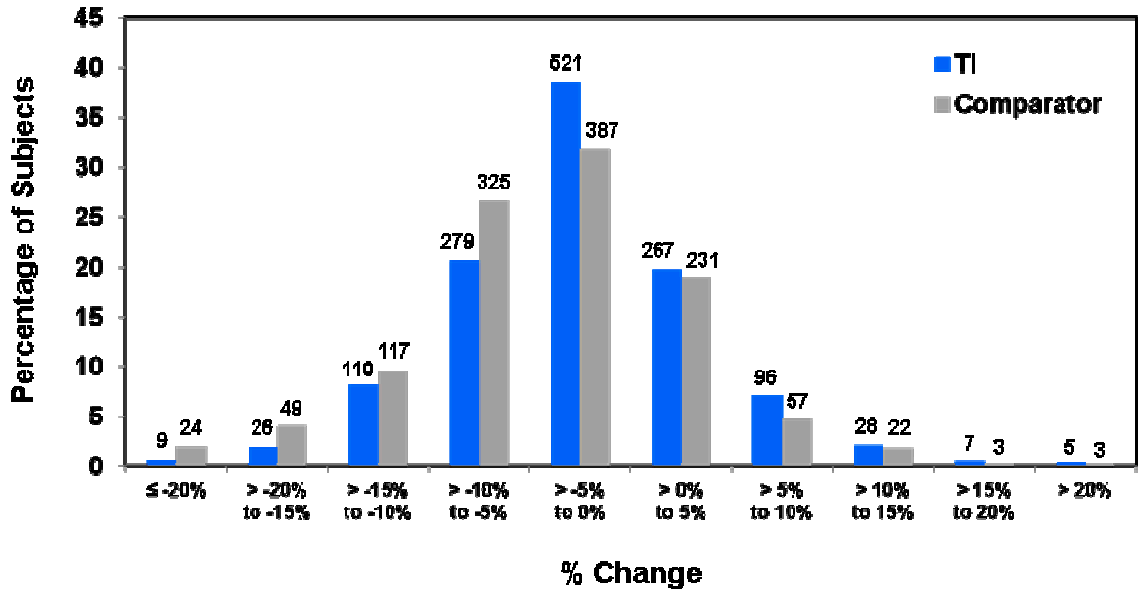
withdrawal of consent, followed by AEs. No association was found between safety parameters, such as cough, and PFT findings between patients who withdrew early as compared to completers. More TI patients with the largest drops in lung function completed the study than usual care patients, suggesting that patients did not drop out due to decreases in lung function.

To assess the effect of dropouts on the statistical inferences, in addition to the mixed model repeated measure (MMRM) model, which is a mixed-effects maximum likelihood based model, data were also analyzed using a series of pattern-mixture (PM) models that account for dropout status and its interactions with other covariates. PM models demonstrated that pulmonary function test results did not differ significantly between completers and subjects who discontinued, and confirmed the robustness of MMRM analysis. Multiple Imputation (MI) analysis was also employed and the results were consistent with MMRM.

POTENTIAL IMPACT OF OUTLIERS

To evaluate potential effects of outliers on the observed mean FEV_1 changes from baseline, the distribution in the percentage change from baseline in mean FEV_1 values at Months 3, 6, 12, 24, and the last measurement was analyzed (Figure 30). More subjects treated with TI had declines from baseline in FEV_1; however, the pattern of the response was similar for both treatment groups with most subjects experiencing small changes. The observed changes in mean FEV_1 were not based on a small number of subjects with large changes (outliers) but rather on small changes experienced by many subjects. The results were similar with subjects with T1DM and T2DM evaluated separately.

Figure 30: Distribution in Percentage Change from Baseline at the Last FEV_1 Measurement for the Pooled Combined T1DM and T2DM PFT Population



Trials contributing to the pooled PFT population: MKC-TI-009, MKC-TI-030, and MKC-TI-102.

SUBJECTS WITH PULMONARY FUNCTION TEST FINDINGS

In the pooled PFT population, a similar number of TI-treated subjects (21.7%) and comparator-treated subjects (23.2%) had PFT findings (a ≥15% decrease from baseline in FVC, FEV_1, TLC, or DL_{CO}) at some time during the trials. The overall numbers of subjects with T1DM or T2DM who reported TEAEs or SAEs were similar regardless of whether or not the subjects had PFT findings at any time during the trial (Table 44). The number of respiratory AEs was higher in the TI group than the comparator group, but this was expected because of the higher frequency of cough in TI-treated patients. Discontinuation due to a PFT finding was rare and reported in only 3 subjects treated with TI (1 with T1DM and 2 with T2DM).

Table 44: All TEAEs, All SAEs, Respiratory TEAEs, and Respiratory SAEs in Subjects with and without Pulmonary Function Test Findings – Combined T1DM and T2DM PFT Population

System Organ Class Preferred Term	TI with Finding (n = 522)	Comparator with Finding (n = 451)	TP with Finding (n = 10)	TI without Finding (n = 1877)	Comparator without Finding (n = 1492)	TP without Finding (n = 104)
Any causality						
TEAEs	442 (84.7)	380 (84.3)	8 (80.0)	1377 (73.0)	1116 (74.8)	65 (62.5)
SAEs	60 (11.5)	48 (10.6)	0	141 (7.5)	135 (9.0)	2 (1.9)
Respiratory						
AEs	201 (38.5)	42 (9.3)	6 (60.0)	615 (32.6)	163 (10.9)	23 (22.1)
SAEs	1 (0.2)	1 (0.2)	0	8 (0.4)	1 (0.1)	0

Notes: Each subject is counted only once per system organ class and preferred term combined. Percentages are based on the total number of subjects in each treatment & finding group in the Safety Population (N).

SUBGROUP ANALYSES

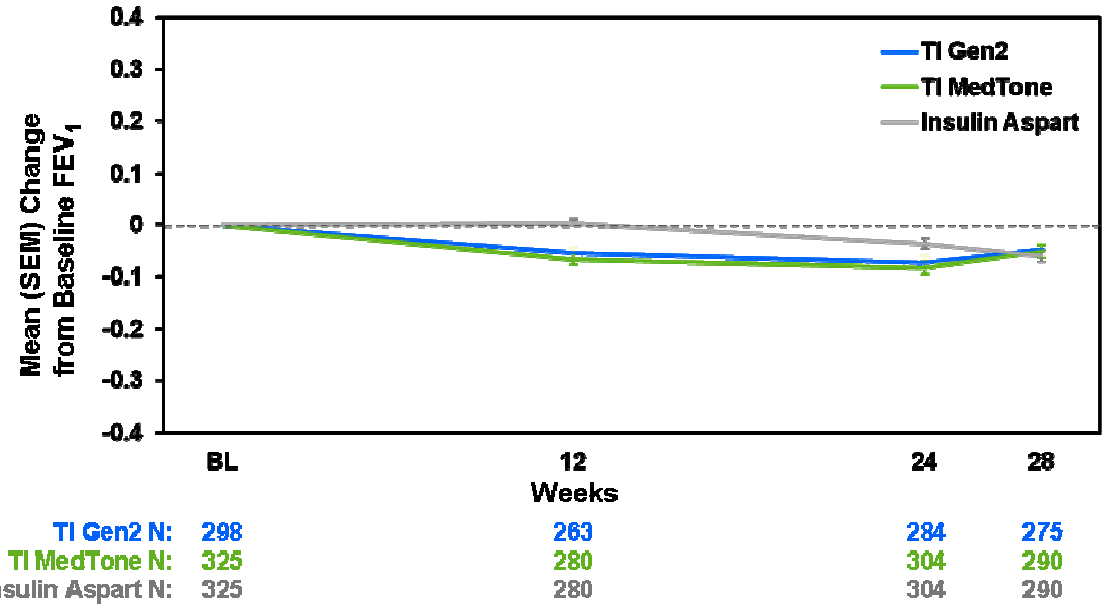
Subgroup analyses for the pooled PFT population were conducted. No consistent patterns were observed in mean changes in FEV_1 from baseline across age categories, (< 25, 25 to 39, 39 to 65, and > 65 years), race (Caucasians were 80% of the population), or gender in either treatment group. The change in FEV_1 from baseline showed no noteworthy pattern with regard to the average daily dose of TI or whether the subject experienced cough.

9.5.6.2 Trial 171 in T1DM

In Trial 171 (T1DM), a head-to-head comparison of the MedTone and Gen2 inhalers was conducted. Mean change from baseline to Week 24 (end of treatment) and Week 28 (follow-up) in FEV_1 in TI-treated subjects was nearly identical regardless of inhaler (Figure 31 and Table 45). As in the pooled PFT population, all treatment groups (both TI groups and the comparator group) experienced small declines in FEV_1 during the treatment period although the declines were greater for the TI groups. However, by 4 weeks after discontinuing TI treatment, the FEV_1 changes from baseline for all 3 treatment groups were similar, indicating the reversibility of FEV_1 effects of TI treatment. To assess the effect of

dropouts on FEV_1 changes, a pattern-mixture (PM) model was fitted with the FEV_1 data to evaluate the significance of interactions among treatment, time and discontinuation patterns (completers vs early termination); results indicated that early dropouts had no impact on the evaluation of FEV_1. Overall, the magnitude and pattern of changes in lung function over a 24-week treatment period were similar in the TI Gen2 and TI MedTone groups.

Figure 31: Mean (SEM) Change from Baseline in FEV_1 (Liters) over Time in T1DM Subjects (Trial 171 Safety Population)



Abbreviations: BL=baseline, FEV_1=forced expiratory volume in 1 second; N=number of subjects; SEM=standard error of the mean.

Table 45: Adjusted Mean Change in FEV_1 (L) in T1DM Subjects from Baseline to Week 24: Gen2 versus MedTone (Trial 171 Safety Population)

Parameter	TI Gen2	TI MedTone
FEV_1 (liters)		
Number of Subjects	127	133
Adjusted Mean (SE)	3.35 (0.028)	3.35 (0.028)
Adjusted Mean Change from Baseline (SE)	-0.07 (0.012)	-0.08 (0.012)
Treatment Difference: Gen2 – MedTone		
Adjusted Mean Change (SE)	0.01 (0.016)	--
95% CI	(-0.02, 0.04)	--
p-value	0.5364	--

Abbreviations: CI=confidence interval; FEV_1=forced expiratory volume in 1 second; SE=standard error.

Consistent with results from the pooled PFT population, in Trial 171, no noteworthy or consistent patterns were observed in the change from baseline in FEV_1 across patient characteristics including gender, age, race/ethnicity, average daily dose of TI, and cough status.

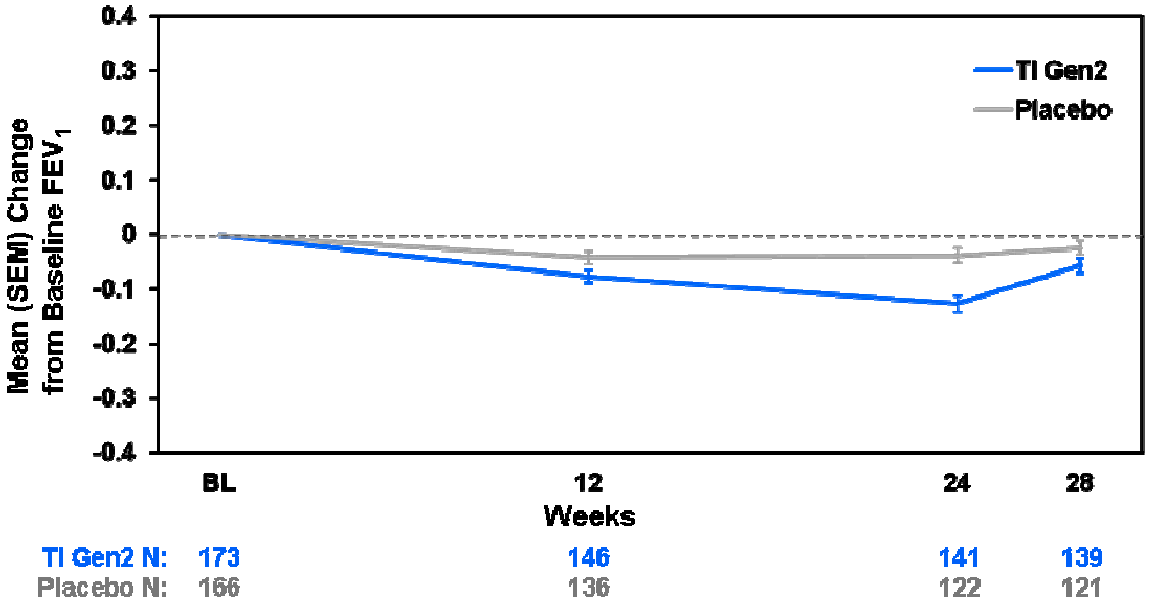
PFT findings (>15% decline from baseline in FEV_1) were uncommon and noted in only 4 subjects (1 TI Gen2, 2 TI MedTone, 1 comparator); none of these subjects discontinued due to PFT findings.

Results for FVC were consistent with the FEV_1 results.

9.5.6.3 Trial 175 in T2DM

The TI Gen2 group showed greater decline in the mean change from baseline in FEV_1 at Week 24 compared to the placebo group (Figure 32). The small treatment group differences in FEV_1 noted at Week 24 resolved by Week 28 (4 weeks after stopping treatment). By Week 28, the changes in baseline in FEV_1 were similar in the 2 treatment groups, indicating that the effect of TI on FEV_1 was reversible. Results were similar in the trial completer population, suggesting that there was no effect of early dropouts on FEV_1 results.

Figure 32: Mean (SEM) Change from Baseline in FEV_1 (Liters) over Time in T2DM Subjects (Trial 175 Safety Population)



Abbreviations: BL=baseline, FEV_1=forced expiratory volume in 1 second; N=number of subjects; SEM=standard error of the mean.

No noteworthy or consistent patterns were observed in the change from baseline in FEV_1 across subject characteristics, including gender, age, race/ethnicity, average daily dose of TI, and cough status.

FVC results were consistent with FEV_1 results.

Results in Trial 175 in T2DM were consistent with those for the pooled PFT population (T1DM and T2DM combined) and Trial 171 in T1DM.

9.5.7 Radiological Findings

The pooled chest x-ray data for subjects with either T1DM or T2DM did not show increased radiologic abnormalities in TI subjects compared with subjects treated with usual care. No safety signal was noted. Similarly, the HRCT and MRI data did not detect clinically significant changes from baseline with long-term use of TI.

9.5.8 Subjects with Underlying Lung Disease

Long term safety of TI in patients with underlying lung disease such as asthma and COPD has not been established. Based on adverse event results from small clinical pharmacology studies in non-diabetic subjects with asthma (Trial 113) and in non-diabetic subjects with COPD (Trial 015), MKC is proposing to contraindicate the use of TI in patients with DM and chronic lung disease such as asthma or COPD.

The controlled Phase 2/3 studies contributing to the 2013 Resubmission Safety Population excluded subjects with underlying lung disease such as asthma and COPD. Limited data for subjects with asthma or COPD, available from other trials (Trial 015 [non-diabetics with COPD], Trial 027 [diabetics with asthma], Trial 105 [diabetics with asthma], Trials 113 and 134 [diabetics with either asthma or COPD]), are presented in this section.

In addition, two subpopulations with mild, subclinical lung dysfunction based on PFT results were retrospectively identified in trials that included baseline PFTs before and after bronchodilator treatment.

- Subclinical Reversible Airway Lung Dysfunction: subjects at least 18 years old with significant improvement or reversibility (defined as ≥12% and 200 mL from before to after bronchodilator) in FEV_1
- Subclinical Fixed Obstructive Lung Dysfunction: subjects over 40 years old with a history of smoking and post-bronchodilator FEV_1/FVC <70%

A total of 172 subjects were identified based on these criteria: 101 subjects with subclinical reversible airway lung dysfunction and 61 subjects with subclinical fixed obstructive lung dysfunction. Results are presented in Sections 9.5.8.3 and 9.5.8.4.

9.5.8.1 Subjects Diagnosed with Asthma or COPD

The long term safety of TI in subjects with COPD and asthma is not currently known, but is being evaluated in ongoing Trial 134. Pulmonary safety results from small clinical pharmacology trials in subjects with asthma and COPD are summarized below.

ASTHMA (TRIAL 113)

This Phase 1, open-label, non-randomized, controlled clinical pharmacology trial was done to evaluate the PK of TI in subjects with asthma and to examine whether the PK profile is altered after pre-treatment with salbutamol and after methacholine challenge-induced bronchospasm followed by salbutamol. Seventeen non-diabetic subjects with asthma and

13 non-diabetic subjects with normal lung function, matched for age, gender, and BMI, were enrolled. Five subjects withdrew prematurely; 25 subjects completed the trial. TEAEs were noted in 82% and 94% of the non-asthmatic and asthmatic subjects, respectively, with cough being the most frequent TEAE (85% vs 71%). Three subjects with asthma discontinued the trial due to AEs (2 due to SAEs of bronchospasm, and 1 due to AEs of nausea and vomiting).

When asthma medications were withheld (short-acting bronchodilators for 6 hours and long-acting bronchodilators for 24 hours), after a single dose of TI, subjects with asthma had a mean decline in FEV_1 of approximately 12% and 6% at 15 and 30 minutes, respectively. A 3.4% decrease in FEV_1 was noted in non-asthmatic subjects at 15 minutes. FEV_1 recovered spontaneously in most subjects by 120 minutes. However, 5 (29%) of 17 subjects with asthma developed bronchoconstriction, wheezing, or asthma exacerbation after receiving TI. These conditions were relieved with bronchodilator therapy. In 2 of these subjects, FEV_1 decreased by 33% and 45% from baseline, and they discontinued the trial due to SAEs of asthma exacerbation:

- A 54-year-old Caucasian man in the United Kingdom experienced wheezing after receiving a single 45 U dose of TI. Eighteen minutes after TI, his FEV_1 decreased 45% from baseline. He was treated with 400 μg of salbutamol with relief of symptoms. Thirty minutes after TI, his FEV_1 had recovered to 4% less than his baseline. The subject was permanently discontinued because of the event.
- A 44-year-old Caucasian man in the United Kingdom experienced bronchoconstriction after receiving a single 45 U dose of TI. Fifteen minutes after TI, his best FEV_1 was 2.04 L (a 33% decrease from baseline). His FEV_1 was 71% of predicted at Screening with mild obstruction. The event resolved and spirometry returned to baseline after treatment with 400 μg of salbutamol.

When TI was given after pretreatment with salbutamol in subjects with asthma, no decline in FEV_1 was noted after TI inhalation.

ASTHMA (TRIAL 027)

This was a 2-part trial. The first part was a parallel, open-label, single-dose trial comparing lung function using serial spirometry in subjects with T2DM with (n=5) and without (n=15) asthma. The second part was a parallel, prospective, controlled, open-label trial with a euglycemic clamp procedure before and after a 7-day TI treatment period to evaluate the bioavailability and tolerability of TI in T2DM subjects with and without asthma.

No clinically meaningful change from baseline in either FEV_1 or FVC was observed in either group. No significant PFT findings were noted. No asthma episodes were reported for the asthmatic group. No pulmonary or asthma-related TEAEs were reported for either group. Cough was reported in 3 asthmatic subjects (60%) and 7 nonasthmatic subjects (47%).

ASTHMA (TRIAL 105)

In Trial 105, prematurely terminated for lack of enrollment, only 3 subjects with asthma and diabetes (both T1DM and T2DM permitted) received treatment (2 TI and 1 comparator). The

2 TI-treated subjects discontinued the trial due to TEAE of asthma and/or coughing. No analyses were done.

COPD (TRIAL 015)

This was a Phase 1b, single-dose, open-label, controlled, hyperinsulinemic, euglycemic clamp trial of TI in non-diabetic subjects with and without COPD. Twenty subjects with COPD and 20 without COPD were matched for age, gender, and BMI. Before and after the TI dose, FEV_1 was evaluated by serial spirometry in a subset of subjects with and without COPD (8 in each group). In contrast to subjects without COPD, those with COPD had a small decline in FEV_1 immediately (at 18 minutes) after inhalation of TI followed by gradual, spontaneous improvement over the next 8 hours. Mean FEV_1 declined from baseline by 8.27% (range 3% to 15%) at 18 minutes, 6.65% at 35 minutes, 7.06% at 65 minutes, 5.6% at 125 minutes, and 3.8% at 485 minutes after TI inhalation. In subjects without COPD, the corresponding values were improvement of 1.75% at 18 minutes, 1.6% at 35 minutes, 1% at 65 minutes, 1.43% at 125 minutes, and 0.5% at 425 minutes.

TEAEs were reported in a similar percentage of subjects with (77.8%) and without (75%) COPD. The most common TEAE in both groups was mild cough. Cough was related to TI and was reported by 12 of 18 subjects (66.7%) with COPD and 14 of 20 subjects (70.0%) without COPD. The cough episodes were typical of those seen after inhalation of a dry powder.

ASTHMA AND COPD (TRIAL 134)

In ongoing Phase 3 Trial 134 (T1DM or T2DM with either asthma or COPD), as of 03 Feb 2014, 17 subjects (9 asthma and 8 COPD) have been randomized (8 to TI and 9 to usual care). Eight subjects have discontinued (6 randomized [3 asthma, 3 COPD] to TI and 2 randomized [1 asthma, 1 COPD] to usual care) and 9 subjects remain on treatment (TI: 1 asthma and 1 COPD subject; the usual care group: 4 asthma and 3 COPD subjects).

Among the subjects with COPD, 2 subjects treated with TI had TEAEs of pulmonary exacerbation. Both subjects discontinued the study. One of these subjects, a 72-year-old male ex-smoker with T2DM, reported increased cough from the first week after initiating TI therapy and developed pulmonary exacerbation of moderate severity on Day 27. TI treatment was interrupted during the exacerbation and subsequently discontinued by the Investigator due to lack of efficacy and pulmonary exacerbation. The second subject, an 80-year-old woman with T2DM, developed pulmonary exacerbation on Day 84. She withdrew consent after the exacerbation and discontinued the trial.

Among the subjects with asthma, 1 TI-treated subject (67-year-old woman with T2DM) was diagnosed with B-cell lymphoma. She also developed an SAE of bowel obstruction subsequently and was discontinued from the study due to the event. The Investigator considered the SAE to be unlikely related to TI.

9.5.8.2 Subjects who Smoke

In Trial 016, 12 smokers (mean age 49.1 years; 83% male) and 12 nonsmokers (mean age 49.7 years; 58.3% male) participated. After a single dose of TI, there was no statistically significant mean change from baseline in either FEV_1 or FVC for either smokers or nonsmokers. Additionally, there were no meaningful changes in mean FEV_1 and FVC within groups during the trial. Slightly more subjects in the smokers group (7 subjects) experienced cough due to inhalation of TI than did non-smokers (5 subjects).

9.5.8.3 Subjects with Subclinical Reversible Airway Dysfunction

The safety population in the pooled Phase 2/3 controlled clinical studies submitted in the 2009 Original NDA included 4467 subjects. Of this Safety Population, a total of 101 subjects (50 in TI group, 49 in the comparator group, and 2 in TP group) met the criteria for subclinical reversible airway dysfunction (Section 9.5.8).

In this small cohort of retrospectively identified subjects, the TEAE profile was reassuring. Cough was the most common respiratory TEAE in the TI group with incidence of 30.0% which was similar to the cough incidence of 26.7% in the general TI-treated population. Excluding cough, the incidences of respiratory AEs were comparable between treatment groups. No AE of bronchospasm was reported. Changes in FEV_1 from baseline were unremarkable in either treatment group.

9.5.8.4 Subjects with Subclinical Fixed Obstructive Lung Dysfunction

Sixty-one subjects (38 in the TI group, 21 in the comparator group and 2 in the TP group) met the criteria for fixed obstructive subclinical lung dysfunction (Section 9.5.8). In this small cohort of retrospectively identified subjects, both TI and comparator groups had similar incidences of TEAEs and SAEs with no respiratory SAEs reported. Cough occurred in 21.1% of TI-treated subjects. The number of subjects with PFT data was small and limited meaningful interpretation of the results.

9.6 Cardiovascular Safety

There has not been an established causal association between long-term insulin use and CV risk. TI represents an alternate means of supplying insulin, but because it is not a distinctly different insulin molecule, there should be no new, distinct issues of CV risk with its use. The FDA issued a guidance document in 2008 that pertained to new anti-diabetic therapies under development, "Guidance for the Industry Concerning Evaluating Cardiovascular Risk in New Antidiabetic Therapies to Treat Type 2 Diabetes."[43] At that time, a significant portion of the TI clinical development program had already been completed; therefore, the trials included in the analyses reported in the original 2009 Original NDA were not designed to evaluate CV risks and trials did not selectively recruit "high risk cardiovascular patients."

The Sponsor presented an analysis using clinically relevant Medical Dictionary for Regulatory Activities (MedDRA) preferred terms (PTs) for cardiovascular (CV) and cerebrovascular events reported within the TI clinical database (2009 Original NDA, Sections 7 and 8). The PTs were selected and analysis was performed by the independent

consulting firm UBC. UBC screened all the MedDRA PTs in the TI safety database, beginning with a list of all standard PTs associated with cardiac disorders, vascular disorders, general and administration site conditions, or surgical and medical procedures system order classes (SOCs). This approach identified a potential inclusive list of PTs for CV and cerebrovascular events. From these PTs, 2 physicians blinded to the subjects' trial drug exposure, independently narrowed the list to PTs that were potentially applicable for retrieving cases. This approach identified a list of PTs for CV and cerebrovascular events provided in Appendix 11 and Appendix 12, respectively. The 2009 Original NDA data demonstrated no clinically significant imbalance between TI and comparator groups for cardiovascular (CV) events. The upper bound of the 2 sided 95% CI for the estimated risk ratio (RR) of important CV events was < 1.3.

For the 2013 Resubmission Safety Population, in order to address the intent of FDA guidance documents and to provide consistency comparing the 2013 Resubmission data with the 2009 Original NDA, 3 analyses were conducted as agreed upon with the FDA:

- Broad Analysis of Cardiovascular Treatment-Emergent Adverse Events: An analysis of CV TEAEs using the same broad set of MedDRA PTs as the 2009 Original NDA.
- Custom Analysis of Cardiovascular Treatment-Emergent Adverse Events: An analysis of CV TEAEs based on an abbreviated list of MedDRA PTs focusing on CV death, nonfatal myocardial infarction (MI), and nonfatal stroke. This custom analysis used the MedDRA screening terms employed by the FDA for the evaluation of saxagliptin[44] as listed in Appendix 11.
- Analysis of Cerebrovascular Treatment-Emergent Adverse Events: An analysis of cerebrovascular TEAEs using the same MedDRA PTs as the 2009 Original NDA.

9.6.1 Broad Analysis of Cardiovascular Treatment-emergent Adverse Events

The incidence of all CV TEAEs in the 2013 Resubmission Safety Population is shown in Table 46. Within each type of diabetes, the incidence of these events was similar between TI and comparator groups. No safety signal was detected for any of the individual PTs. For the combined T1DM and T2DM population, 216/3017 subjects (7.2%; exposure-adjusted incidence rate 10.5 per 100 subject-year exposure [SYE]) in the TI group and 175/2198 subjects (8.0%; exposure-adjusted incidence rate 8.1 per 100 SYE) in the comparator group reported at least 1 CV event. No safety signal was detected for any of the individual PTs. An increased risk for a CV event was not seen with TI use in the T1DM, T2DM, or combined population as expressed by RRs ranging from 0.80 to 0.98 for the TI group compared with the comparator group (Table 47 and Table 49).

Table 46: Cardiovascular TEAEs by Broad Analysis by Diabetes Type and Treatment (2013 Resubmission Safety Population)

CV Event	T1DM		T2DM		
	TI [N=1026] [SYE=697] n (%)	Comparator [N=835] [SYE=778] n (%)	TI [N=1991] [SYE=1356] n (%)	TP [N=290] [SYE=98] n (%)	Comparator [N=1363] [SYE=1374] n (%)
Any TEAE, n(%)	40 (3.9)	37 (4.4)	176 (8.8)	10 (3.4)	138 (10.1)
Any TEAE, n/100 SYE	5.7	4.8	13.0	NC	10.0

Abbreviations: NC=not calculated; SYE=subject-year exposure.

Table 47: Broad Analysis of Relative Risk of Cardiovascular TEAEs with TI vs Comparator (2013 Resubmission Safety Population)

Diabetes Type	Number of TI Subjects (Events)	Number of Comparator Subjects (Events)	RR (CI)
Type 1 Diabetes	1026 (40)	835 (37)	0.80 (0.53,1.22)
Type 2 Diabetes	1991 (176)	1363 (138)	0.98 (0.81,1.19)
Type 1 and Type 2 Diabetes	3017 (216)	2198 (175)	0.96 (0.80,1.14)

Abbreviations: CI=confidence interval; RR=Relative Risk.

9.6.2 Custom Analysis of Cardiovascular Treatment-Emergent Adverse Events

The incidence of major CV TEAEs in the 2013 Resubmission Safety Population is presented for T1DM and T2DM combined in Table 48. A total of 10/3017 (0.3%; exposure-adjusted incidence rate 0.5 per 100 SYE) subjects in the TI group and 14/2198 (0.6%; exposure-adjusted incidence rate 0.7 per 100 SYE) subjects in the comparator group reported such events.

Table 48: Custom Analysis of Cardiovascular TEAEs for T1DM and T2DM Combined (2013 Resubmission Safety Population)

Preferred Term	TI [N=3017] [SYE=2052] n (%)	TP [N=290] [SYE=98] n (%)	Comparator [N=2198] [SYE=2152] n (%)
Any TEAE	10 (0.3)	1 (0.3)	14 (0.6)
Cardiac Disorders	8 (0.3)	0	8 (0.4)
Myocardial infarction	6 (0.2)	0	7 (0.3)
Acute myocardial infarction	2 (0.1)	0	1 (0.0)
Nervous System Disorders	3 (0.1)	1 (0.3)	6 (0.3)
Cerebral infarction	1 (0.0)	0	0
Cerebrovascular accident	1 (0.0)	0	5 (0.2)
Haemorrhagic stroke	1 (0.0)	0	0
Ischaemic stroke	1 (0.0)	1 (0.3)	1 (0.0)

Abbreviations: SYE=subject-year exposure.
Note(s):
Each subject is counted only once per system organ class and preferred term combined. TEAEs listed in the table include 4 subjects in the TI group and 1 subject in the comparator group who died due to the CV event.

An increased risk for a cardiovascular event was not evident with TI use in the combined T1DM and T2DM population, as expressed by the relative risk of 0.58 with an upper bound of the 95% CI of 1.26 (Table 49). The 95% CIs are wide because of the small number of events when analyzed separately for T1DM and T2DM.

Table 49: Custom Analysis of Relative Risk of Cardiovascular TEAEs with TI vs Comparator (2013 Resubmission Safety Population)

Diabetes Type	Number of TI Subjects (Events)	Number of Comparator Subjects (Events)	RR (CI)
Type 1 Diabetes	1026 (1)	835 (3)	0.37 (0.04,3.57)
Type 2 Diabetes	1991 (9)	1363 (11)	0.61 (0.27,1.38)
Type 1 and Type 2 Diabetes	3017 (10)	2198 (14)	0.58 (0.27,1.26)

Abbreviations: RR=Relative Risk; CI=confidence interval.

9.6.3 Analysis of Cerebrovascular Treatment-Emergent Adverse Events

For T1DM and T2DM combined, the incidence of cerebrovascular TEAEs was low and similar between TI and comparator subjects. There were 37/3017 (1.2%) subjects in the TI group and 29/2198 (1.3%) in the comparator group who reported at least 1 event. Loss of consciousness, the most frequently reported cerebrovascular TEAE, was noted in 14 (0.5%) subjects in the TI group and 10 (0.5%) subjects in the comparator group.

9.7 Neoplasms

9.7.1 All Malignant Neoplasms

9.7.1.1 All Malignancies

A method to evaluate events reported as malignant was created by UBC, independent consultants blinded to trial treatment, who created a MedDRA search strategy (Appendix 13) for the 2009 Original NDA. In the 2013 Resubmission, events reported as neoplasms were identified using the same MedDRA (Version 15.1) search strategy and were summarized by SOC including the preferred term (PT) referring to either benign or malignant neoplastic disease. These events were reviewed by MKC to identify malignant and benign neoplasms. A comprehensive medical review of individual cases of malignant neoplasms was conducted, focusing on time to onset (latency; <90 or ≥90 days after initiation of trial treatment), tumor type, clinical course, and subject disposition.

In the Phase 2/3 controlled clinical trials, malignant neoplasms (excluding non-melanoma skin cancers) occurred in 13 (0.43%) subjects who received TI and 8 (0.32%) subjects who received comparator (7 who received active comparator and 1 who received TP [placebo]) for incidences per 100 patient-years of 0.63 (95% CI [0.34, 1.08]), and 0.35 (95% CI [0.13, 0.67]), respectively (Table 50). In addition, six non-melanoma skin cancers (5 basal cell cancers and 1 squamous cell cancer of the nose) occurred in 4 TI-treated and 2 comparator-treated subjects.

In the Phase 2/3 controlled clinical trials, the observed malignancies showed heterogeneity of tumor types with no concentration in a specific type of cancer and no clustering by organ system. Overall, the pattern is one that would be expected in this age group. No unusual pattern of occurrence emerged in this analysis. The anatomic locations and type of cancers observed in the clinical trials were consistent with the types most commonly observed in the diabetic population and did not exceed the expected background incidence in the general US population based on the Surveillance, Epidemiology, and End Result (SEER) database, 2000-2010.[42] It is important to note that the SEER database for the general US population does not account for the presence of diabetes and smoking status. Thus, it may underestimate the incidence of overall cancer in diabetes population.

Table 50: Number of Subjects with Malignant Neoplasms in the Controlled Phase 2/3 Clinical Trials (2013 Resubmission Safety Population, T1DM and T2DM Combined)

Cancer Type	TI (N=3017) 2052 SYE	Comparator (N=2198) 2152 SYE	TP (N=290) 98 SYE
Breast cancer	4	2	0
Prostate cancer	3	1	0
Colon cancer	1	1	0
Ovarian epithelial cancer	1	0	0
Bile duct cancer	1	0	0
Cervix carcinoma	0	1	0
Rectal cancer	1	1	0
Metastatic gastric cancer	1	0	0
Pancreatic carcinoma	0	1	0
Neuroendocrine tumor (SCLC)	1	0	0
Squamous cell carcinoma of palate	0	0	1
Incidence (%)	13 (0.43)	7 (0.32)	1 (0.34)
Incidence per 100 patient-years (95% CI)	0.63 (0.34, 1.08)	0.35 (0.13, 0.67)	1.02 (0.03, 5.69)

Abbreviations: CI=confidence interval; N=number of subjects; SYE=subject-year exposure; TI=Technosphere Insulin; TP=Technosphere particles (placebo, no insulin); SCLC= Small cell lung cancer.
Note: This table excludes non-melanoma skin cancers (3 patients in TI group and 2 patients in the comparator group had diagnosis of basal cell carcinoma of skin).
Note: Cancer cases in ongoing Trials 134 and 139 are not included in this table. Information for these trials can be found in Sections 9.5.8.1 and 9.11.2, respectively.

Six additional non-basal cell malignancies were reported in an uncontrolled clinical trial in subjects with T2DM (Trial 010). The cancer types were prostate (2 cases) and pancreatic, renal, bronchogenic, and chronic lymphocytic leukemia (1 case each). The mean (SD) duration of exposure to TI was 30.1 (11.98) months for a total exposure of 574 subject-years.

9.7.1.2 Lung Malignancies

Lung malignancies are of particular interest due to the route of administration (inhaled) of TI. In the TI clinical program, there was 1 case of a neuroendocrine tumor (small cell carcinoma) involving the lung in controlled Trial 102 and a second case of non–small cell bronchogenic carcinoma in uncontrolled extension Trial 010. Both of these cases were reported in the 2009

Original NDA. Both of these subjects were ex-smokers with a smoking history of 40 pack-years.

TRIAL 102 SUBJECT 2909: NEUROENDOCRINE TUMOR (SMALL CELL CARCINOMA OF THE LUNG)

A 62-year-old Caucasian male in Argentina with T2DM and history of heavy smoking (40 pack-years) was randomized to receive TI and sc insulin glargine starting on 07 Aug 2007. His medical history included cancer of the rectum treated with partial resection of the colon and radiation therapy to the pelvis and chemotherapy. At the time of trial entry, the subject was in follow-up care. On 05 Dec 2007, the subject presented with an elevated plasma CEA level. Physical examination showed an enlarged neck lymph node. Computed tomography (CT) scan of the thorax revealed right lung hilar lymphadenopathy and right mediastinal lymph node enlargement. On 21 Dec 2007, the subject discontinued trial drug and was withdrawn from the trial. On 21 Feb 2008, biopsy of the cervical lymph node showed neuroendocrine type "oat cell" (small cell) carcinoma. He was hospitalized on (b) (6) and died on (b) (6). Neither autopsy information nor a death certificate was provided. The investigator assessed causality as not related to trial treatment.

TRIAL 010 SUBJECT 3316: BRONCHIAL CARCINOMA

A 66-year-old male, in the Czech Republic with T2DM and history of heavy smoking (40 pack-years), occupational exposures to toxic agents, and a family history of lung cancer (father died of lung cancer) was first randomized on 03 Nov 2004 to 42 U of TI. At Visit 2 on 26 Oct 2004 and Visit 12 on 17 Feb 2005, he had a tiny, chronic nodule in the right upper lobe of the lung. The subject finished participation in the parent trial and entered extension Trial 010 on 21 Mar 2005. On 09 Aug 2006, the subject was found to have microcytic anemia. A CT scan of the thorax in April 2006 was negative. On 07 Dec 2006, CT scan of the lungs showed 2 focal lesions measuring 12 x 19 x 20 mm and 19 x 14 x 20 mm in right lung and enlarged mediastinal lymph nodes. TI was discontinued and the subject withdrew consent. On 02 Feb 2007, biopsy showed non-differentiated bronchogenic carcinoma (non-small cell). The subject died in (b) (6). Neither autopsy information nor a death certificate was provided. In the opinion of the investigator, the causality for the bronchogenic carcinoma was unlikely related to trial drug.

BACKGROUND INCIDENCE RATES

An independent pharmacoepidemiologic group (RTI Health Solutions) conducted a review of the scientific literature to identify published estimates of the incidence of lung cancer in patients with diabetes and, where feasible, reported lung cancer incidences stratified by smoking status.

The only trial of patients with diabetes, controlled for smoking, reported an incidence of 0.5 to 0.7 per 1,000 person-years among nonsmoking, postmenopausal women aged 50 to 79 years.[45] In the general population, the incidence of lung cancer among nonsmokers at its highest was 0.21 (95% CI, 0.14 0.31) per 1,000 person-years.[46] In the general population of smokers, the incidence of lung cancer varies substantially by age and by number of cigarettes smoked per day. In the age groups of 45-69 years, (age group of most of the TI group in the clinical trials), lung cancer incidence per 1,000 person-years was 2.2 in men and women

combined.[47] In a trial that stratified by number of cigarettes smoked, and age groups, the incidences of lung malignancies were 1.8 cases per 1,000 person-years in men and 1.5 cases per 1,000 person-years in women.[48] In summary, most lung cancer incidences reported in the literature, either adjusted or pooled incidences among men and women or among men only (smokers and nonsmokers) with diabetes, fall within the range of 1 to 2 cases per 1,000 person-years.

COMPARISON OF INCIDENCE RATES IN THE TI TRIALS VERSUS BACKGROUND

Among all TI users in the controlled and uncontrolled clinical trials (excluding 18 to 24 year old subjects), there were 2 lung cancer cases during 2,622 person-years of follow-up for an absolute incidence of 0.8 cases (95% CI, 0.09-2.8) per 1,000 person-years in subjects treated with TI in clinical trials; this incidence is consistent with the rate expected in a population of patients with diabetes comprised of nonsmokers and ex-smokers, as noted above.

CASES REPORTED AFTER COMPLETION OF CLINICAL TRIAL PARTICIPATION

Two additional cases of lung malignancy were reported after the completion of participation in Trials 030 and 010.

A 59-year-old Caucasian man (Trial PDC-INS-0008 Subject 358) started participation in Trial PDC-INS-0008 on 11 Jun 2004, and was randomized to receive TP. Baseline HRCT showed a small pleural based nodule at RLL and left lingular opacity. Pleural nodule remained unchanged at last HRCT in Feb 2008. At the conclusion of trial, the subject enrolled in the open-label, uncontrolled, extension Trial 010 and received TI from 22 Oct 2004 to 21 Apr 2008. The duration of treatment was 3 years, 5 months, and 30 days. On 16 Nov 2010, approximately 2.5 years after completion of all therapy with TI, the subject developed symptoms of cough, throat tickle, intermittent fever, and hoarseness of voice and was noted to have left vocal cord paralysis. Diagnostic evaluation included CT of the chest which revealed a large mass in the middle mediastinum at the level of carina extending into AP window and azygous and subcarinal lymph nodes. Bilateral, needle aspiration biopsy from the paratracheal lymph nodes showed poorly differentiated non-small cell lung cancer favoring squamous cell carcinoma (stage unspecified). He was a non-smoker (experimented with smoking during college), and worked in the trucking industry. His family history included a father with a history of colon cancer who died at age 51 and a brother with history of prostate cancer at age 76.

A 73-year-old, non-smoking female with T2DM received TI from 21 Apr 2006 to 02 Mar 2008 while participating in clinical Trial 030. Chest X-rays on 20 Apr 2006, 28 Mar 2007, and 05 Mar 2008 were unremarkable. The subject initiated anti-diabetic treatment with insulin glargine at the end of the trial and did not participate in any other clinical trial. In July or Aug 2011, almost 3.5 years after completing treatment with TI, during an annual examination, chest fluorography revealed a shadow in the lungs. On 24 Oct 2011, spiral CT of the chest revealed a 55 mm x 48 mm mass of uneven density with distinct tortuous borders in the left lower lobe partly deforming the left lower lobe bronchi. Chest showed enlarged lymph nodes: paratracheal, up to 8 mm; paraaortic, up to 12 mm; at bifurcation, 10 mm; and bronchopulmonary, up to 9 mm. She also had a left-sided pleural

effusion. The subject did not seek medical follow-up until developing severe dyspnea in December 2011. On (b) (6), the subject was hospitalized. On (b) (6), an oncologist provided a diagnosis of central cancerous tumor (bronchogenic cancer) of the left lung (T3 NX M0, Stage II) and pleuritis. In the opinion of the investigator, a causal relationship between the event and the trial medication the subject received during the clinical trials could not be excluded.

Since completion of the studies, 2 voluntary reports of lung cancer cases were received. These 2 lung cancer cases were spontaneously reported 2.5 and 3.5 years after the subjects had discontinued trial participation. In the absence of a systematic follow-up, and given the lack of control group, information related to medical treatment or new risk factor exposure data since trial completion, it is difficult to ascertain causality. In addition, it is difficult to ascertain rates, as this very uncertain numerator is based only on voluntary reporting.

9.7.2 All Non-Malignant Tumors

9.7.2.1 Benign Neoplasms

In the Safety Population, 32 (1.06 %) of 3017 TI-treated subjects, 1 (0.34%) of 290 TP-treated subjects, and 24 (1.09%) of 2198 subjects treated with comparator drugs reported benign neoplasms. An additional 6 subjects reported benign tumors in uncontrolled Trial 010. The reported benign tumors occurred in varied anatomic sites with no evidence of clustering by site. A listing of all subjects with benign tumors is provided in Appendix 14.

9.7.2.2 Pulmonary Nodules

Focal radiological findings of lung masses/nodules/lesions on HRCT/MRI or chest X-ray were noted in 10 (0.33%) of 3017 TI-treated subjects, 4 (0.18%) of 2198 comparator-treated subjects, and 2 (0.69%) of 290 subjects in the TP group. Careful review of these cases, including follow-up serial imaging studies, showed that in all of these cases, nodules were small and either remained unchanged in size or appearance or disappeared in subsequent imaging studies or turned out to be calcified granulomas. None of these radiological findings were identified as lung malignancies. Appendix 14 provides a list of these events.

9.8 Anti-Insulin Antibodies

Development of anti-insulin antibodies (IABs) has been a clinical observation and a clinical concern from the advent of insulin therapy. It has been seen with both insulin analogs and recombinant human insulin. It is reported to occur to a greater extent in subjects treated with an inhaled insulin product as opposed to sc insulin, reflecting a higher immunogenic response that occurs when proteins are absorbed from the pulmonary tract. In most large population trials, IABs have not been correlated with measures of efficacy or insulin dose requirements. Insulin antibodies that are secondary to pulmonary exposure to insulin are not different in regards to clinical outcomes than those produced after parenteral administration of insulin, even with higher absolute values.

For the IAB analysis, the same pooling strategy used in the 2009 Original NDA was used for the 2013 Resubmission. Results of the IAB analysis are summarized separately for subjects with T1DM and T2DM. The newly completed Phase 3 trials are presented individually, followed by the pooled results. As different comparators were used in different trials of different duration, the individual trial results are considered primary for this evaluation.

The concentration of insulin-binding immunoglobulin G (IgG) IABs in serum was assayed by Bio Analytical Research Corporation (BARC) using the same validated radioimmunoassay used in all previous trials. Anti-insulin antibodies are reported in Kronus U/mL. Clinical outcomes, such as change in HbA1c, change in FPG, and TEAE (including immunogenic TEAEs) rates in subjects with high IAB concentrations were reviewed. The relationship between change in IAB concentration and end-of-trial clinical parameters (HbA1c level, FPG level, and total insulin dose) were examined using Spearman's correlation coefficient and p-value analyses for each individual trial (Trials 009, 030, 102, 171, and 175). Data from controlled Phase 2/3 trials were pooled at 3-month, 6-month, 12-month, and 24-month time intervals as shown:

- For T1DM, pooled correlation analyses included subjects from the following trials:
  - Trials 009, 030, and 101 at 3 months
  - Trials 009, 030, and 171 at 6 months
  - Trials 009 and 030 at 12 months
  - Trial 030 at 24 months.
- For T2DM, pooled correlation analyses included subjects from the following trials:
  - Trials 005, 014, 026, 030, 102, and 103 at 3 months
  - Trials 014, 030, 102, 103, and 175 at 6 months
  - Trials 030 and 102 at 12 months
  - Trial 030 at 24 months.

9.8.1 Anti-Insulin Antibodies in T1DM Subjects

In Trial 171, the median IAB concentrations were similar between treatment groups at baseline. At Week 24, median IAB values increased by approximately 3-fold in the TI Gen2 group (median value at baseline 9.30 Kronus U/mL and 30.85 Kronus U/mL at Week 24) and by approximately 5-fold in the TI MedTone group (median value 8.60 Kronus U/mL at baseline and 41.10 Kronus U/mL at Week 24); they remained essentially unchanged in the comparator group (sc insulin aspart) (median value 8.70 Kronus U/mL at baseline and 8.90 Kronus U/mL at Week 24). Clinical review of individual data for subjects with the greatest increases in IAB levels (ie, subjects in the top 10^{th} percentile) did not reveal incidence or pattern of TEAEs different from that of the entire trial population.

Data from the pooled trials were consistent with results from Trial 171. The mean and median IAB values increased from baseline by approximately 3-fold and 4.5-fold in TI Gen2 and TI MedTone groups, respectively; minimal increases were noted in the sc insulin comparator group. After discontinuation of therapy, IAB titers returned towards normal within several months; however, the follow-up period was not sufficiently long to determine if levels returned completely back to baseline. In the clinical impact analysis, no relationship

was noted between change in IAB and reduction in glycemic parameters, insulin dose, incidence of potentially immunogenic TEAEs, or incidence of SAEs. Comparison of TEAE incidence for subjects in the 95th and 5th percentile of maximum post-baseline IAB levels did not detect any discernible patterns or adverse trends.

9.8.2 Anti-Insulin Antibodies in T2DM Subjects

In Trial 175, in insulin-naïve subjects with T2DM poorly controlled with OADs, a minimal increase in median IAB concentrations (5.8 to 7.4 Kronus U/mL) was noted at Week 24 in the TI group. As expected, there was no change in IAB levels in the placebo group.

Data from the pooled analysis showed similarly low IAB increases with treatment in the TI group. When compared with subjects receiving sc insulin, the median change from baseline in IAB concentrations was 1.8 versus 2.9 Kronus U/mL for TI group and comparator groups, respectively. In the clinical impact analysis, no association was noted between IAB levels and clinical outcomes such as HbA1c, FPG, insulin dose, SAEs, and immunogenic TEAEs. No clinical consequences of elevated IAB levels were noted by analysis of absolute values, 95th percentile, or subjects with the highest IAB values.

9.9 Adverse Events of Special Interest

9.9.1 Diabetic Ketoacidosis (DKA)

For the 2013 Resubmission Safety Population, the incidence of DKA was 0.46% (0.68 per 100 subject-years) in the TI group and 0.23% (0.33 per 100 subject-years) in the comparator group. In the 2009 Original NDA, 2 long-term trials suggested an imbalance of DKA events in T1DM subjects, prompting careful ongoing surveillance. In Trial 009, a trial of 1-year duration, 8 TI-treated subjects and no subjects receiving comparator treatment had SAEs of DKA. In Trial 030, a trial of 2-year duration, SAEs of DKA were reported in 5 TI-treated subjects and 3 comparator-treated subjects. Most DKA events were related to concurrent infection and treatment interruption and/or reduced dosing. With reinforced investigative site education, no new cases of DKA have been reported since the 2009 Original NDA. A listing of DKA events is provided in Appendix 15.

9.9.2 Potential Immunogenic Events

The analysis of potential immunogenic events was not done prior to the 2013 Resubmission; therefore, MedDRA PTs for potential immunogenic events (Appendix 16) were pre-specified only in newly completed Phase 3 trials. The 2013 Resubmission Safety Population TEAE database was searched for these specific PTs and potential immunogenic TEAEs were analyzed. The incidence of potential immunogenic TEAEs in the combined T1DM and T2DM population was 2.4% in the TI group, 2.4% in the TP group, and 1.5% in the comparator group. The most common potential immunogenic TEAEs in the TI group were myalgia (0.9%) and wheezing (0.5%). Most events reported as drug hypersensitivity in all treatment groups were exacerbation of pre-existing allergies, and were mild to moderate in severity. There was no safety signal in the incidence, distribution, or severity of potential immunogenic events reported with TI. Differences in the incidence of potential immunogenic

events between the TI and comparator groups were predominantly due to TEAEs related to the respiratory system. Inhalation of the dry powder itself may cause such TEAEs (like wheezing) without being immunogenic events.

9.9.3 Adverse Events of the Eye

During the review of the 2009 Original NDA, an imbalance in eye disorders, specifically retinal detachment, vitreous hemorrhage, and eye hemorrhage, was noted. Since the original submission, a single new case of eye hemorrhage has been reported in a TI Gen2 subject with T1DM. No new cases of retinal detachment were reported since the 2009 Original NDA. In the 2013 Resubmission Safety Population, for T1DM and T2DM combined, the overall incidence of ophthalmic TEAEs was low and similar between the TI (0.3%) and comparator (0.4%) groups. There were no potential signals related to eye events in TI subjects.

9.10 Laboratory Evaluations, Vital Sign Measurements, and ECGs

In Phase 2/3 clinical trials, hematology, clinical chemistry, and urinalysis tests were performed by a central laboratory. Prior to the initiation of each trial, the central laboratory supplied MKC with a list of reference ranges, units of measurement, and laboratory certifications. During the trial, the PI reviewed all out-of-range and "alert" laboratory values for clinical significance. The results presented are for the 2013 Resubmission Safety Population.

No clinically meaningful changes were noted in any of the clinical laboratory variables (excluding glucose). The percentage of subjects who had clinically important laboratory values was small and generally balanced between the treatment groups. No subject discontinued treatment due to a laboratory abnormality. No TI-treated subject had liver function test results that met Hy's Law criteria for hepatotoxicity.

No clinically meaningful changes in any vital signs (body temperature, pulse, respiration rate, and blood pressure) occurred.

There was no consistent signal of an effect of TI on ECG measurements.

9.11 Subpopulations and Ongoing Trials

9.11.1 Subpopulations

In the 2013 Resubmission Safety Population, no meaningful difference or new safety signal was found for TEAEs related to drug-drug interactions (DDIs) with metformin or sulfonylurea drugs; too few subjects were using dipeptidyl peptidase 4 (DPP-4) inhibitors with TI to draw meaningful conclusions.

Potential drug-demographic interactions in the 2013 Resubmission Safety Population were evaluated by analyzing TEAEs (excluding hypoglycemia) for safety signals by age, sex, race, BMI, baseline HbA1c, early discontinuation status, and geographic region. No safety signal resulting from an interaction was identified. The analysis of TEAEs by BMI showed increasing incidences of TEAEs with increasing BMI across all treatment groups, with no

clear inter-group differences noted. The patterns and incidences of TEAEs varied geographically. For the TI group in T1DM and T2DM combined, lower incidences of TEAEs were noted for subjects in Eastern Europe than for those in North America, Latin America, or Western Europe.

9.11.2 Ongoing Trials

Trial 134 is an ongoing Phase 3 trial to evaluate the long-term safety (12-month treatment period and a 2-month follow-up) of TI Inhalation Powder in patients with T1DM or T2DM and underlying COPD or asthma. Preliminary safety data are presented in Section 9.5.8.1.

Trial 139 is an ongoing Phase 3 open-label trial to evaluate the safety of TI in subjects with T1DM or T2DM who converted from Exubera® to TI due to the marketing discontinuation of Exubera (September 2008). Enrollment is complete with 16 subjects. As of 31 Jul 2013, there were 11 SAEs reported by 6 subjects. All SAEs were considered unrelated to either treatment or device use. There was 1 reported death due to complications related to leukemia. As of 03 Feb 2014, an additional SAE (bladder cancer recurrence) was reported in a subject with a history of bladder cancer.

Two single-dose PK Trials 178 and 179 are ongoing in healthy non-diabetic subjects. As of 03 Feb 2014, 40 subjects in Trial 178 and 36 subjects in Trial 179 have received TI. No death or SAE has been reported. No new safety issues or concerns have been noted.

9.12 Safety Conclusions

TI is well tolerated with a safety profile not unlike that of marketed insulin products and/or dry powder inhalers. The most common AE (excluding hypoglycemia) noted in the clinical trials was a mild, transient cough occurring shortly after TI inhalation. This cough lessened over time as patients adjusted to inhaling a dry powder. As noted in clinical trials, TI use was associated with mild, non-progressive, and reversible decreases in pulmonary function (FEV_1). In a small study in subjects with asthma, bronchospasm or a worsening of asthma, as well as a decrease in FEV_1, were noted after TI administration if asthma medications were withheld. Premedication with a bronchodilator before TI administration prevented both of these reactions. Nevertheless, given the reactions of some asthmatic subjects to TI administration without bronchodilator premedication, TI use will be contraindicated in people with asthma, COPD, or other chronic lung disease per proposed product labeling. Incidence of observed malignancy (overall and lung) did not exceed the expected background incidence in the general and diabetic population. A greater increase in the production of IABs was observed after TI treatment (T1DM>T2DM) compared with sc insulin treatment; IAB concentrations decreased towards baseline after treatment discontinuation. As has been previously noted across a large population of insulin users, no adverse clinical consequences could be associated with IAB development. There were no safety signals with regards to CV safety, overall DKA incidence, immunogenicity, ocular events, laboratory tests (excluding glucose), vital signs, or ECGs.

10 BENEFIT-RISK AND RISK MANAGEMENT

Diabetes increases the risk of disabling and life-threatening microvascular and macrovascular diseases. It is also a major cause of premature mortality including CV death. Despite the importance of glycemic control in reducing morbidity and mortality, the majority of diabetic patients do not achieve recommended glycemic targets. Although the effectiveness of insulin is not disputed, there is considerable delay in initiating insulin therapy when glycemic control is suboptimal, and once insulin therapy is initiated, there are numerous barriers to optimized use of insulin therapy and compliance with appropriate use in both T1DM and T2DM patients. Thus, new treatment options are needed to help address the unmet medical need of timely initiation and effective maintenance of insulin therapy. TI, an efficacious, convenient, easy to use, ultra-rapid acting inhaled insulin is an important additional treatment option for patients with diabetes, especially those for whom hypoglycemia is a problem, weight gain is an issue, or injections are a barrier to insulin use.

10.1 Benefits Associated with TI Treatment

TI provides a new therapeutic option in T1DM and T2DM management. TI has been tested against placebo and active comparators representative of the current standard of care. It has been evaluated in clinical trials across a broad spectrum of diabetes severity: insulin-naïve T2DM subjects with inadequate glycemic control on OADs, insulin-requiring T2DM subjects, and T1DM subjects utilizing a MDI basal/bolus regimen. Its unique PK/PD profile more closely mimics endogenous prandial insulin secretion compared with currently available RHIs and RAA insulins, thereby offering patients and HCPs flexible and convenient meal-time insulin dosing in a non-injection delivery system. Clinical trial data demonstrate glycemic efficacy, reduced hypoglycemia, weight neutrality, and consistently positive patient preference.

10.1.1 Unique Pharmacokinetics and Pharmacodynamics

TI is characterized by an ultra-rapid onset and shorter duration of action compared with both regular and rapid acting analog insulin. This has been consistently demonstrated throughout the development program in both normal subjects and in adult T1DM and T2DM subjects. No clinically significant drug interactions have been noted; renal dysfunction, hepatic dysfunction, asthma (with bronchodilator premedication before TI administration), COPD, bronchodilator administration, and upper respiratory tract infection do not influence TI pharmacokinetics. Dose proportionality has been demonstrated, and TI administered using the Gen2 inhaler and the previous MedTone inhaler are bioequivalent.

The rapid absorption of insulin administered as TI is very similar to first-phase endogenous insulin secretion.[11] This early secretory response is critical in maintaining normal glucose homeostasis and its loss precedes and predicts diabetes. The first-phase insulin secretion rapidly shifts metabolic processes from the fasting to the prandial state (eg, from glucose production to glucose disposal) by increasing tissue insulin levels and suppressing endogenous glucose production.[11] Indeed, following a meal challenge, rapid suppression of endogenous glucose production has been demonstrated with TI.

From a patient's perspective, the time-action profile of TI allows for simpler and more flexible mealtime dosing, lessens the potential for inter-prandial hypoglycemia, and enables additional prandial dosing to decrease meal-time glycemic excursion, when needed.

10.1.2 Demonstrated Glycemic Efficacy

In clinical trials, across a broad spectrum of diabetes severity, TI has been shown to be noninferior to active comparators and superior to placebo in HbA1c reduction, as demonstrated in 3 of the four 24 to 52-week clinical trials in both T1DM and T2DM subjects. The glycemic-lowering effect has been durable as noted in the trials of 52 weeks' duration. Target HbA1c goal attainment with TI was significantly better than with placebo and, as expected in noninferiority trials, TI and insulin comparators, on the whole, were similar in their target achievements. A greater decrease in FPG with a TI plus basal insulin regimen than with comparator insulin therapies has been a consistent finding. Seven-point glucose profiles demonstrated that TI reduced prandial glycemic excursions.

10.1.3 Reduced Hypoglycemia

Hypoglycemia as a consequence of insulin or insulin-secretagogue therapies is an important safety concern for both patients and practitioners. It is also an impediment to optimizing glycemic control. The ADA Workgroup on Hypoglycemia has proposed that a significant reduction by a new drug, device, or management strategy in incidence of severe hypoglycemia (even by as little as 10% to 20%) or a ≥30% reduction in overall hypoglycemia incidence, event rates, or both, would represent a clinically important improvement over existing therapies.[34]

In the 3 trials in insulin-using T1DM and T2DM subjects, TI was associated with significant and/or clinically meaningful decreases in both incidence and event rates of all and severe hypoglycemia. A substantial reduction in severe hypoglycemia event rates was noted in every active-comparator trial (a range of 20% to 65% reduction across the trials). In insulin-naïve T2DM subjects, the incidence of all hypoglycemic events in TI-treated subjects on metformin was not different from the incidence in placebo-treated subjects on metformin and sulfonylurea (SU), a very commonly used therapeutic two-drug combination therapy.

10.1.4 Less Weight Gain

Weight gain with insulin and other OAD therapies is a common unwanted side effect, and the degree of weight gain is an important factor in therapy selection. Overall, in multiple, controlled clinical trials with treatment duration up to 52 weeks in subjects with T1DM and T2DM, a consistent weight advantage for TI versus insulin comparators was noted. The mean baseline BMIs for the trial populations were in the overweight category for subjects with T1DM and in the obese category for subjects with T2DM. In both trials in T1DM subjects, a modest weight loss was noted with TI in contrast to weight gain with comparator insulin. In insulin-using T2DM subjects, TI was associated with a more modest weight gain than comparator over the 52-week trial duration. These data suggest that TI could be a useful addition to insulin therapy options in diabetes, especially in overweight/obese patients requiring CV disease comorbidity management.

10.1.5 Ease of Use

Afrezza is patient-friendly and easy to use. Previous experience with Exubera, an inhaled insulin, highlights the limitations associated with a complicated, large device.[49] In contrast, the Gen2 inhaler is small and TI self-administration using this device is simple. The system relies on the patient's inhalation effort alone to produce a flow rate that delivers TI to the pulmonary tract. The Gen2 inhaler does not require cleaning because it is discarded and replaced after 15 days of use. The summative Human Factors Usability Validation Trial for the Gen2 inhaler included subjects with diabetes with and without previous insulin experience; subjects with color-blindness, retinopathy, and neuropathy; as well as health care providers, trained and untrained. The trial demonstrated that the system can be correctly, safely, and effectively used by the intended user population. The device, packaging, labeling, and associated Instructions for Use (IFU) are validated and do not lead to any patterns of confusion, failures, errors, or patient safety risks. These data show that TI is a non-injected insulin delivery system that is safe and easy to use.

10.1.6 High Patient Preference Ratings

Trials have suggested that patients with diabetes are likely to prefer inhaled insulin over injected insulin, in some cases by a ratio of 8:1.[50] The overwhelming majority of recently surveyed PCPs believe that patients would be more willing to use insulin if no injection was involved.[24] In a multi-center patient use trial with TI, overall, subject ratings of their experience with TI were consistently positive (median: 93% positive ratings), including improved attitudes toward insulin therapy and high treatment satisfaction.[51]

10.2 Safety Including Identified and Potential Risks

TI safety has been evaluated in more than 6500 adults over the course of this program: 3017 subjects were exposed to TI, 290 subjects were exposed to TP, and 2198 subjects were exposed to comparator treatments in the controlled clinical trials with continuous exposure of >14 days.

10.2.1 Overall Adverse Event Profile

The non-respiratory adverse events observed with TI were similar to those observed with insulin therapy in general, including increases in anti-insulin antibody titers that were not associated with any clinical consequences. Adverse events, with the exception of cough, were similar in incidence and type between TI-treated subjects and those treated with non-inhaled comparators. TI use was associated with approximately 21% excess incidence (versus comparators) in a mild to moderate, intermittent, dry cough that usually occurred within 10 minutes of inhalation. The excess incidence of cough declined to approximately 2% by the third month of treatment. Overall, 2.8% of subjects discontinued clinical trial participation due to cough. The characteristics of the cough were consistent with stimulation of the cough reflex by dry powder inhalation that decreased as subjects become accustomed to dry powder inhalation.

10.2.2 Pulmonary Function

The TI development program included careful and rigorous PFT assessments using a standardized testing and quality control program with PFT laboratories certified by MKC and all tests subject to independent, blinded, central review. Overall, in long-term assessments, the treatment differences in mean change from baseline in FEV_1 between the TI and comparator groups were small, occurred early (within the first 3 months of treatment), were non-progressive over 2 years (least squares mean difference, was -40 mL at 3 months and -45 mL at 24 months), and disappeared upon discontinuation of TI therapy, irrespective of duration of TI exposure. In TI subjects, no noteworthy or consistent patterns in FEV_1 change were noted across subject demographics, including gender, age, and average daily TI dose. Head-to head comparison of the previous MedTone and the current Gen2 devices showed no significant difference in terms of pulmonary safety between the inhalers (Trial 171).

10.2.3 Tolerability in Subjects with COPD or Asthma

A large clinical trial assessing pulmonary safety of TI in subjects with COPD and asthma patients is currently underway. Limited data are available regarding the use of TI in subjects with underlying lung disease. In a clinical pharmacology study, 5 of 17 subjects with asthma in whom asthma medications were withheld developed bronchoconstriction, wheezing, and/or asthma exacerbation upon receiving TI. Symptoms were relieved promptly with bronchodilators. In patients with COPD in a Phase 1 trial, serial spirometry showed ~9% mean acute decline of FEV_1 after a single dose of TI. Based on the available safety data, proposed labeling will contraindicate TI use in patients with asthma, COPD or other chronic lung disease.

10.2.4 Cardiovascular Safety

There has not been an established causal association between long-term insulin use and CV risk. TI represents an alternate means of supplying insulin, but because it is not a distinctly different insulin molecule, there should be no new, distinct issues of CV risk with its use. However, because patients with diabetes are at increased risk for microvascular and macrovascular complications as well as CV death, CV safety was examined across the clinical trials with several analyses that were presented to the FDA for their consideration. No CV safety signals were found.

10.2.5 Neoplasms

In the nonclinical and clinical development programs, cancer risk was closely examined in light of the potential lung cancer signal in Exubera-treated patients. Both TI and Technosphere particles (placebo, no insulin) were evaluated in a comprehensive nonclinical program. No evidence for carcinogenicity was observed following either 26-week sc administration in transgenic mice or 104-week inhalation in Sprague-Dawley rats. In the Phase 2/3 controlled clinical trials, the incidence of malignant neoplasms (excluding non-melanoma skin cancers) per 100 patient-years was 0.63 (95% CI [0.34, 1.08]) and 0.35 (95% CI [0.13, 0.67]), for the TI and comparator groups, respectively. The anatomic locations and type of cancers observed in the clinical trials were consistent with the types

most commonly observed in the diabetic population and the incidence did not exceed the expected background incidence in the general US population. A pulmonary neuroendocrine tumor (small cell carcinoma) was diagnosed in a 62-year-old male with a past history of colorectal cancer and smoking. Additionally, a non-small cell lung cancer (NSCLC) was diagnosed in a 68-year-old male former smoker with a family history of lung cancer.

There have also been 2 spontaneous reports of lung cancer reported 2.5 and 3.5 years after the subjects had discontinued clinical trial participation. In the absence of a systematic follow-up, and given the lack of control group, information related to medical treatment or new risk factor exposure data since trial completion, it is difficult to ascertain causality. In addition, it is difficult to ascertain rates, as this very uncertain numerator is based only on voluntary reporting. To evaluate the long-term risk of lung cancer, a postmarketing observational cohort trial is planned.

10.2.6 Treatment Initiation

Each TI cartridge containing 10 U or 20 U of insulin approximates 3 units or 6 units of sc insulin, respectively. The proposed Afrezza label uses these approximate insulin doses to transition patients from injected insulin to TI therapy, or to switch from TI back to injected insulin, if needed. Also, the approximate insulin dose is a reference point that enables the TI cartridge to conform to traditional insulin units. Labeling the cartridge in this way gives patients, and prescribers, perspective for their initial inhaled TI dose relative to their experience with sc insulin. As with all insulin therapy, changing from a familiar regimen to a new one (ie, adding TI as prandial insulin or switching from prandial sc insulin/RAA to TI) can result in an initial deterioration in glycemic control. TI should be titrated for the individual patient to achieve glycemic control with doses limited only by the risk of hypoglycemia. Other insulin therapy, OAD therapy, and glucose monitoring may also need to be adjusted.

10.3 Risk Management

10.3.1 Respiratory Tract

Patient education will be helpful in advising patients of the characteristics and transient nature of cough, should it occur. Labeling will state that patients using TI who experience persistent or recurring cough should be carefully evaluated, including spirometry as medically appropriate, to ensure that any underlying pulmonary pathology is detected in a timely manner.

TI use will be contraindicated in patients with asthma, COPD or chronic pulmonary disease. Warnings and precautions will be included in the label for patients who smoke or who have discontinued smoking less than 6 months prior to starting TI therapy. Healthcare professionals will be instructed that prior to initiating therapy with TI, all patients should be clinically evaluated with a detailed medical history, physical examination, and spirometry (FEV_1) to identify any potential underlying lung disease.

There are no known predictors of patients who might experience >15% decline in pulmonary function with therapy. However, labeling will recommend repeat on-therapy testing at the discretion of the health care provider for patients with increasing or persistent cough or wheezing or the new onset of bronchospasm or breathing difficulties or other unexplained respiratory symptoms. These risks will be defined in the Dear Healthcare Professional Letter (DHCPL) included in the Risk Evaluation and Mitigation Strategy (REMS) Communication Plan for TI.

A REMS program will be used to guide patient selection and management. MKC will implement a Communication Plan as part of the REMS. The plan includes a DHCPL. In addition to HCPs, the letter will be distributed to professional organizations and societies. The intended audience for the Communication Plan is HCPs who are likely to prescribe TI. The targeted HCPs will be prescribers who have written at least 1 prescription for a medication used to treat diabetes in the past 12 months and will include endocrinologists and internal medicine, family, and general practitioners. MKC will issue a DHCPL to targeted HCPs within 60 days of REMS approval or within 60 days of product commercialization if product launch occurs >60 days after REMS approval. The DHCPL will convey the key risk message of respiratory difficulty immediately post-inhalation, especially in patients with chronic lung disease.

10.3.2 Neoplasms

In the clinical program of a previously marketed inhaled insulin product Exubera, a lung cancer incidence imbalance was noted (Exubera-treated versus control subjects, 0.13 cases per 100 subject-years versus 0.03 cases per 100 subject-years, respectively).[52] All cases occurred in former smokers, but there were too few cases to determine whether the emergence of these events was related to Exubera. In the post-approval surveillance program (FUSE) [53] requested by regulatory authorities and conducted over a 2-year period, including events that occurred at any time from the start of the clinical program, there was no increase in either primary lung cancer mortality (the primary endpoint) or all-cause mortality. However, the incidence ratio for primary lung cancer data was 3.75 (95% CI [1.01-20.68]). The FUSE investigators concluded that these data were indicative of a potential, but inconclusive, increased risk of lung cancer, and the observed trend toward the increased risk may be explained by reporting/detection bias associated with preferential screening and reporting of cases for subjects exposed to Exubera in the original studies, a promotional effect of Exubera inhalation among smokers, or some combination of these factors. If real, the absolute increase in the risk of lung cancer was small.

The incidence of lung cancer in subjects treated with TI in clinical studies is consistent with the rate expected in a population of patients with diabetes comprised of nonsmokers and ex-smokers. However, to evaluate the long-term risk of lung cancer, a postmarketing observational cohort trial is planned. The primary objective of the study will be to determine the incidence of primary pulmonary malignancies in patients taking TI. Secondary objectives will be to determine the incidence of all other malignancies (except non-melanoma skin cancers), serious pulmonary events, serious allergic events, and serious hypoglycemic events. Approximately 1,800 patients will be enrolled and followed for at least 5 years (approximately 8,000 person-years of follow-up exposure). Enrolled patients will be

followed for the duration of the study or until withdrawal from participation or death. Follow-up will continue even if Afrezza therapy is discontinued. For sample size purposes, a background rate of 64.6 pulmonary malignancies per 100,000 person-years of surveillance was utilized, based on population-based data from National Cancer Institute Surveillance, Epidemiology and End Results (SEER).[42] The study will provide additional quantification and characterization of potential adverse events with low incidence or long latency after exposure to Afrezza. In addition, the study will help identify adverse events that may occur outside of the controlled clinical trial setting.

10.3.3 Deterioration in Glycemic Control

To manage the potential deterioration in glycemic control, labeling will reinforce how to transition patients from injected prandial insulin to treatment with TI. Patients will be advised that any change of insulin should be made cautiously and only under medical supervision. As with all insulins, changes in insulin strength, manufacturer, type (eg, regular, NPH, analogs), or species (animal, human) may result in the need for a dose change. Concomitant OAD treatment may also require adjustment. Patients with T1DM will also be informed that they must use longer-acting basal insulin with TI prandial dosing to maintain adequate glycemic control. As determined by PK data, no dose adjustment is usually necessary for patients who have a URI and are able to appropriately inhale TI. Patients will be advised not to interrupt therapy for URIs or other symptomatic concurrent illnesses. However, blood glucose monitoring is essential and dose adjustment may be required.

10.3.4 Labeling and Patient Education

TI cartridges will be labeled in units of approximate equivalence to sc administered insulin units as the healthcare providers and patients are familiar with sc injected insulin, such labeling should provide safer transition and dose titration.

In addition to the REMS, other measures will also be employed to ensure proper product usage and to mitigate any risks associated with TI therapy in at-risk populations. Such measures may include:

- Information and demonstration kits for HCPs
- Patient-friendly information, which may include instructions, visual diagrams, and a mechanism to enable patients to practice using the device
- An AFREZZA website available to consumers and HCPs containing prescribing and patient information and a toll-free customer support number

10.3.5 Pharmacovigilance Plan

A pharmacovigilance plan was developed to ensure optimal product usage to manage risks while providing a new insulin therapy available to advance patient care. The objectives of the TI pharmacovigilance plan are:

- To provide pertinent sources of pharmacovigilance data with information regarding the use of TI and any actual or potential adverse drug reactions, medication errors, and product defects
- To describe a plan for addressing actual or potential TI safety issues, including the follow-up of targeted medical events
- To identify and evaluate potential safety signals proactively based on nonclinical, clinical, and postmarketing data
- To maintain product labeling that accurately captures the risks associated with TI while also representing the benefits of the therapy

The pharmacovigilance plan consists of proactive methods to ensure the earliest possible detection and characterization of potential safety signals. This approach requires uniform collection of safety data from all MKC trials worldwide, information systems for warehousing data, and frequent integrated evaluation of safety data from all sources during clinical development and marketed use.

10.4 Overall Conclusions

Afrezza provides a new therapeutic option in the management of both T1DM and T2DM patients. Clinical trials have shown Afrezza to be safe and well-tolerated with a safety profile consistent with its novel mode of insulin delivery. Afrezza results in glycemic control with the added benefit of weight neutrality and reduced hypoglycemia risk compared with other insulin therapies.

Because of its unique PK/PD characteristics, glycemic efficacy, clinically-meaningful hypoglycemia and weight advantages, and its delivery of insulin in an alternative, noninvasive route of administration that provides convenience and ease of use, Afrezza represents a useful addition to the therapeutic options available to patients and HCPs in the management of diabetes. Its safety profile is not associated with any clear safety signals, and potential risks will be better understood based on a comprehensive postmarketing surveillance program. With appropriate labeling of the product and the Sponsor's commitment to identifying and implementing a broad risk management strategy, meaningful clinical benefits can be provided to patients. The favorable benefit/risk profile of TI justifies its use as a novel insulin in diabetes management.

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Appendix 1 American Diabetes Association (ADA) Diabetes Treatment Guidelines

Glycemic Recommendations for Many Nonpregnant Adults with Diabetes

HbA1C	**<7.0%***
Preprandial capillary plasma glucose	70–130 mg/dL* (3.9–7.2 mmol/L)
Peak postprandial capillary plasma glucose†	<180 mg/dL* (<10.0 mmol/L)
*Goals should be individualized based on:	
duration of diabetes	
age/life expectancy	
comorbid conditions	
known CVD or advanced microvascular complications	
hypoglycemia unawareness	
individual patient considerations	
More or less stringent glycemic goals may be appropriate for individual patients	
Postprandial glucose may be targeted if HbA1C goals are not met despite reaching preprandial glucose goals	

†Postprandial glucose measurements should be made 1 to 2 hours after the beginning of the meal when glucose levels generally peak in patients with diabetes.

Source[10]: American Diabetes Association. Standards of Medial Care in Diabetes. Diabetes Care 2014;37:S14-S80.

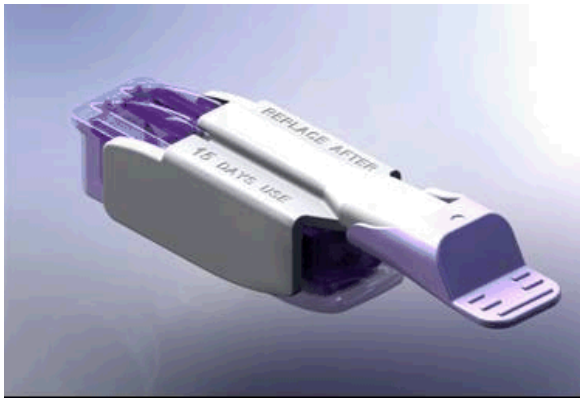
Appendix 2 Human Factors Evaluation of the Gen2 Inhaler

INTRODUCTION

The Technosphere® Insulin (TI) Inhalation System (AFREZZA®) design development program, including the Gen2 Inhaler, cartridges, packaging, labeling and the Instructions for Use included methodology to evaluate human factors/usability principles as described in FDA guidance documents, "Medical Device Safety – Integrating Human Factors Engineering into Risk Management", dated June 18, 2000 and the FDA draft guidance document, "Applying Human Factors and Usability Engineering to Optimize Medical Device Design" dated 22 Jun 2011 and "AAMI/ANSI HE75:2009 Human Factors Engineering – Design of Medical Devices" standard.

The TI Inhalation System incorporates a breath-powered, re-usable Gen2 inhaler (figure below left) in combination with cartridges (figure below right) containing pre-filled amounts of Technosphere® Insulin (TI) Inhalation Powder. To use the system, subjects are required to open the inhaler, load a cartridge, and close the inhaler. The act of closing the inhaler opens the flow path for dosing. The inhalation effort lifts, de-agglomerates, and disperses the TI Inhalation Powder to the pulmonary tract.

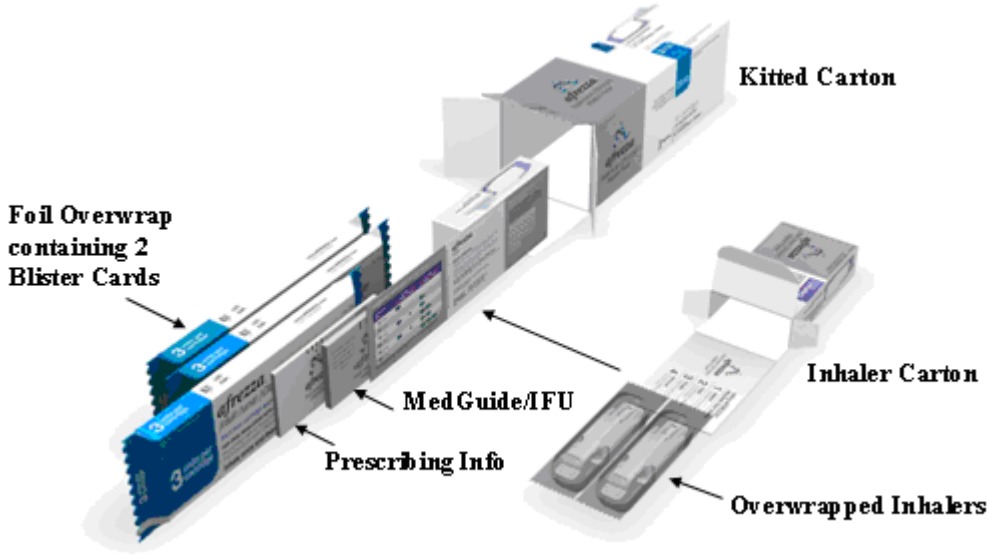
Gen2 Inhaler



Gen2 Cartridges

Packaging for TI Inhalation Powder (figure below) has been designed to promote ease of use and patient compliance. Cartons, foil overwrap, and blister packages prominently identify each cartridge via printed text and utilize blue and green color to emphasize the differences between doses.

Package Configuration - 90 Count 3 Units, 2 Inhalers

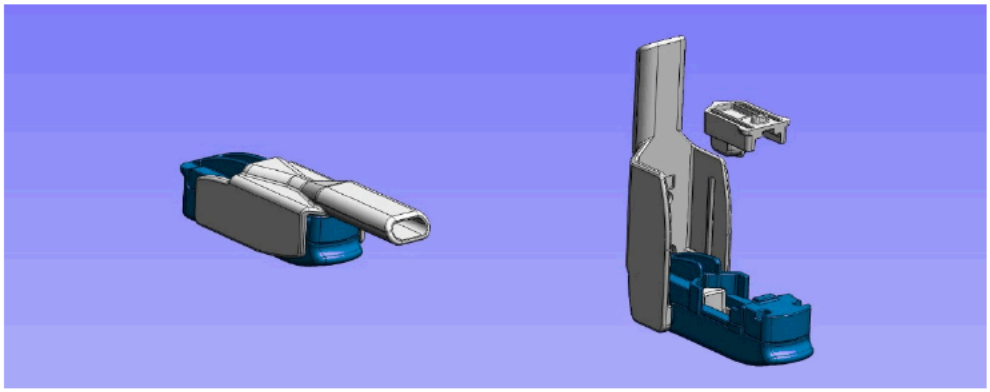


The TI Inhalation System for inhale-able insulin therapy will be used by patients with diabetes mellitus diagnosed as type 1 or type 2 in the adult population (18 years and older). Users are anticipated to possess varying degrees of cognitive ability, dexterity, and visual acuity. In addition, users may also possess other diabetes related complications such as retinopathy and neuropathy for example. To self-administer with the delivery system, patients must be able to manipulate the inhaler and cartridge and be able to inhale through the inhaler when the mouthpiece is placed in their empty mouth. Below is a brief summary of the key parts of the Human Factors research for the development of the Gen2 inhaler,

FORMATIVE TESTING RESEARCH

During early development of the Gen2 inhaler, input on system design, interface points, and usage was gathered from subjects with diabetes. Sample inhalers and empty cartridges were given to subjects in controlled research settings to explore user reaction and acceptance. MLN Research conducted subject interviews using the early Gen2 inhaler (figure below) at the L&E research facility in Raleigh, NC. MKC representatives were present in an observation room. The sessions consisted of six small group interviews, three conducted with women and three with men. In total, seventeen individual subjects (9 women, 8 men) with type 2 diabetes aged 50 years or older were interviewed. All subjects used insulin with daily injections and represented a mix of employment, educational, racial, and ethnic backgrounds.

Gen2 inhaler for the August 2008 focus group



The objective of this research was to observe whether diabetic subjects could easily handle and use the Inhalation System. Opinions and attitudes about the Inhalation System were solicited. Initially, subjects were introduced to the concept of inhaled insulin and given an overview of the TI Inhalation System encompassing the cartridge and the inhaler. They were then told the inhaler opens to allow for cartridge placement but were not shown how to do it. During the interview sessions, subjects were provided with empty cartridges and informed that ultimately insulin would be contained in the cartridges and inhaling through the device would deliver a dose.

After the overview, inhaler and cartridge samples were given to each subject and the formative human factors evaluation began. The session moderator was to use one of three techniques on each group. The first included verbal instruction to the subjects followed by observation. The second technique included visual (no verbal) instruction where pictures/words were shown followed by observation. And, the third technique was to instruct a single subject in the group on how to use the system followed by observation on what happens when that subject instructs the others.

Results of the research were positive. Most of the subjects were able to use the system without any moderator instruction. Overall, subjects were able to easily handle and operate the inhalation system and were very receptive to the idea of using the system for insulin administrations. In particular, the arrow shaped cartridge provided a strong visual cue enabling all respondents to correctly place the cartridge in the inhaler. Subjects were specifically queried on the overall size of the inhaler and cartridge to determine if the system was too small. Overwhelmingly, respondents liked the size. When using the system, subjects naturally grasped the fore and aft location on the inhaler body with their index finger and thumb. As designed, this technique permits easy lifting on the Mouthpiece to open the inhaler. Some respondents were slow to understand how much force was needed to lift the Mouthpiece open. However, once the inhaler was opened a first time, these subjects were able to recognize the force requirement and used the system effortlessly. Subjects suggested that cartridges should be color coded for different strengths. Most agreed the TI Inhalation System offered considerable advantage to their current injection regimens, including needle avoidance, speed of administration, discretion, and convenience.

The next round of formative tests with more respondents and in multiple locations was conducted. These were aimed at determining whether there was an inhaler grip style or aesthetic/design that would foster greater acceptance. Empty cartridges and inhalers of different design were given to subjects for simulated use. Interviews were conducted in Phoenix AZ, Chicago IL, and Boston MA. MLN research moderated the sessions while MKC observed. Subjects were insulin injection users (primarily subjects with type 2 diabetes) ranging in age from 40 - 70 years, and represented a mix of employment, educational, racial and ethnic backgrounds. Two interview sessions were conducted in each city, one session with men and one with women. In total, 45 different subjects (21 women and 24 men) participated.

The formative test sessions conducted in Aug and Dec 2008 resulted in strong support and continued development of the Gen2 inhaler. The simplicity and ease of use provided by the design resonated with prospective subjects. Importantly, the size of both the inhaler and the cartridge were confirmed to be acceptable to users, neither too small nor too large. In addition MKC did not observe any use related challenge for subjects that would indicate a need for redesign. Overall, inhaler grip style at the fore and aft locations of the body was preferred as all subjects used the technique easily to open the device. The observation of simulated use from both test sessions contributed to the development of the IFU.

Formative evaluations with intended users were continued throughout the development of the TI Inhalation System. Evaluations focused on the user tasks with the various components of the packaged product, including the Gen2 Inhaler, cartridges, Instructions for Use (IFU) and printed components. Each evaluation resulted in modification and optimization of the TI Inhalation System components. Using the formative testing approach outlined in the FDA Draft Guidance “Applying Human Factors and Usability Engineering to Optimize Medical Device Design” dated 22 Jun 2011; MKC implemented improvements to the usability of the TI Inhalation System.

USABILITY ASSESSMENTS

Usability tests were conducted on the Gen2 inhaler during the development program to incorporate subject use aspects. This included an evaluation of subject inhalation effort, simulated use studies, a survey of subject experience with clinical usage, a pediatric usability study and a formal usability test for validation purposes.

Background

A potential limitation of some breath-powered inhalers can be evident in the inherent link between inhalation effort and device performance. In use of the Gen2 inhaler, a patient’s inhalation effort must lift, de-agglomerate, and disperse the powder. Given the importance of the inhalation effort and the high resistance attribute of the Gen2 system, understanding what levels of effort subjects exert in use is relevant. For example, too little effort may not be sufficient to generate flows needed for delivery and large efforts may result in flow rates that limit the deposition in the lung (powder impact to the throat). The Gen2 system was designed to be a high-resistance system that is not bound by large inhalation efforts because flow rates are kept low.

Inhalation profiling is accomplished by characterization of pressure versus time or flow versus time curves. Inhalation efforts achieved in use of the Gen2 system have been captured with both naïve subjects (users not experienced with TI or any DPI) using empty cartridges and subjects using TI during administration.

The captured inhalation profiles are complex and typically require the identification of many parameters for complete characterization. These include for example, flow increase rate, peak flow, peak pressure, average pressure/flow following peak, inhalation dwell time, total time, etc. Of these parameters, the most useful are a characteristic pressure drop and corresponding flow curve. Measurements of inspiratory pressure as a function of time provide peak inspiratory pressure (PIP) and, since flow is dependent on pressure in breath-powered inhalers, the area under the pressure time curve ($AUC_{0\text{-time}}$) adequately characterizes the profile.

The characteristic driving force of the Gen2 system is PIP and the impact of this force on the powder is measured by AUC. During an inhalation effort with the Gen2 system, most powder is discharged in the first second and the discharge is complete in two seconds. For these reasons, the peak pressure within the first two seconds, $PIP_{0\text{-}2\ sec}$, and the area under the pressure versus time curve in the first second, $AUC_{0\text{-}1\ sec}$, are the parameters most suitable for characterization of product performance.

Inhalation Efforts

The inhalation efforts from naïve subjects using the system with empty cartridges and from subjects during TI administrations were recorded and characterized. When these inhalation efforts were replicated in the laboratory, product performance was acceptable. Furthermore, testing determined the minimum thresholds to be $PIP_{0\text{-}2\ sec} \geq 2$ kPa and $AUC_{0\text{-}1\ sec} \geq 1.2$ kPa·s. Of the 301 inhalations recorded (MKC-T-140, MKC-TI-141, and MKC-TI-142), 98 % were acceptable, including the efforts by naïve subjects. This indicates that consistent powder performance is easy to achieve with the Gen2 inhaler.

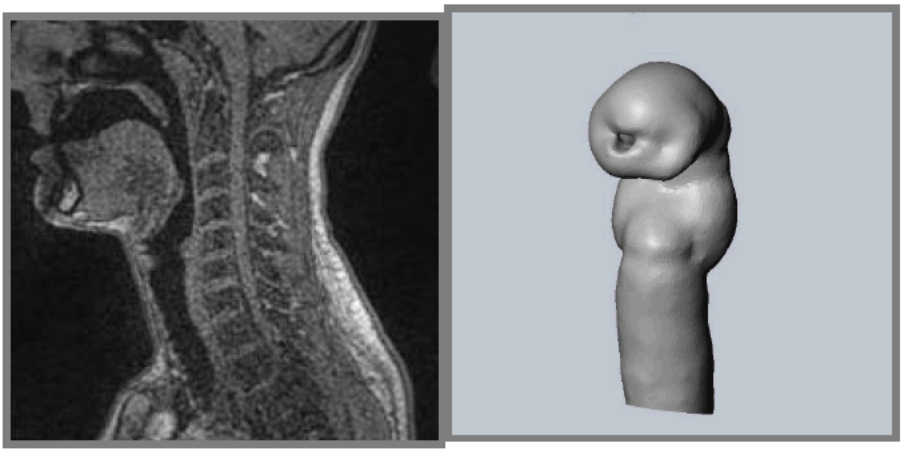
Simulated Use Studies

Compatibility between device performance and patient airway anatomy is an important feature in inhalation devices. For example, large powder particles or powder particles moving too fast are more likely to deposit in the mouth or at back of the throat, thereby reducing the quantity of powder reaching the lungs. Unfortunately, *in vivo* assessment of powder deposition is difficult, so *in vitro* testing incorporating elements of human anatomy has become more common. MKC has developed custom test equipment including an anatomically correct airway model (ACA) from mouth entrance to mid-trachea to better evaluate inhaler performance and resulting deposition patterns.

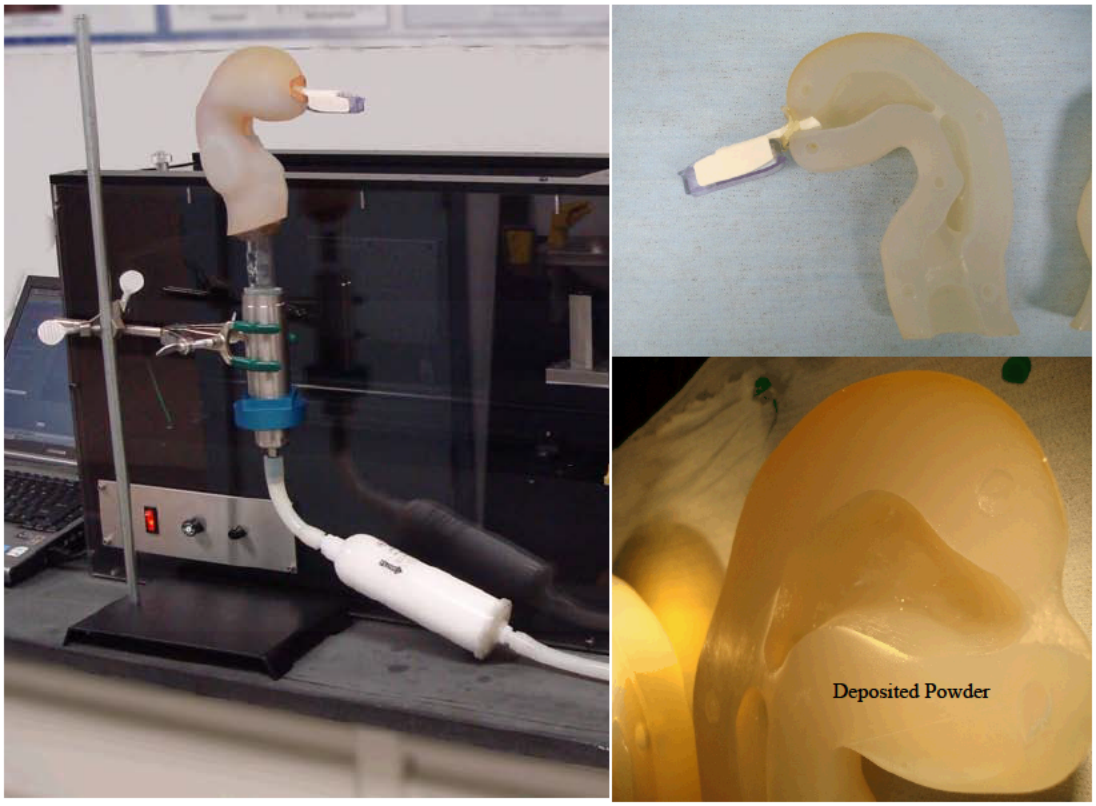
The ACA (figures below) is a stereolithography (SLA) of a healthy male subject. The model was developed based on MRI images of the mouth and throat taken during an inhalation effort. The images were then converted to an SLA prototype consisting of a solid, plastic model with separable halves. Splitting the model into halves aided the visual assessment of

powder deposition patterns and subsequent powder removal between tests. During testing the two halves were held together and sealed.

ACA: MRI Image (left), computer generated solid model (right)



ACA simulation set-up (left), model section (upper right) and deposited powder (lower right)



Powder deposition is measured using gravimetric analysis. To use the system, air is drawn through the ACA by a vacuum pump set at a range of relevant pressures. When the inhaler is sealed in the mouth of the ACA, air will flow through the device and disperse a plume of powder. The powder travels through the model where some of it is deposited on the walls. The remaining, un-deposited powder is collected in a collection tube for gravimetric analysis and deposition is determined by difference. The system was used to assess robustness of the systems at various inhaler inspiratory profile and inhaler orientations.

Pediatric Usability Testing

The Gen2 inhaler was also incorporated into MKC's pediatric plan. A pilot study (MKC-143) was conducted to evaluate the ability of a pediatric population to handle and operate the Gen2 inhaler and to characterize the inhalation profiles with empty cartridges. Five age groups were assessed: 4-5 years (n=14), 6-8 (n=15), 9-10 (n=15), 11-13 (n=15), and 14-17 (n=15).

Subjects were instructed on usage with pictures rather than the IFU pamphlet because of uncertainty in the reading ability of the entire study population. Oral instructions were also provided to help the children interpret the eight steps shown in the pictures. Subjects in all age groups were able to successfully handle and operate the Gen2 inhaler. One subject in the 4-5 year age group failed to lift the Mouthpiece open on the first attempt, probably because the child was fearful of breaking the device. The data indicate that pediatric subjects as young as 4 years of age can exert sufficient inspiratory effort to use the Gen2 inhaler.

VALIDATION TESTING

MKC contracted with Interface Analysis Associates ("IAA") to conduct a validation usability study for the TI Inhalation System (AFREZZA®). The study was conducted to determine if any aspects of the inhaler, cartridge, packaging, labeling, and instruction for use (IFU) lead to confusion, failures, high-risk errors, or patient safety risks. Successful validation was to be demonstrated by the absence of any pattern of failure, error, or user difficulty.

The final inhaler design, including final labeling and packaging, was used in this Summative Human Factors Usability Validation Study. Formative studies indicate no residual risk-oriented design implications. The IFU and labeling incorporate all feedback from the FDA and have been further optimized through subsequent formative tests with minor modifications to the layout, text and illustrations. The protocol for this study was designed to identify any and all significant risks/hazards and was reviewed iteratively with FDA prior to execution. Subsequent to the FDA approval of the protocol, it was amended to include IFU and packaging validation components and utilized the 3 unit and 6 unit product presentations.

The study was conducted with a total of 90 participants (validation study enrolment table) assigned to 1 of 2 training groups: Orientation by Certified Diabetes Educator (CDE) and Un-trained users. All participants completed 3 unaided simulated administrations of 3 different AFREZZA doses (either 3, 12, and 15 units or 6, 9, and 18 units). Evaluation took place over 2 sessions conducted 4 to 24 hours apart under 3 contexts (validation study dosing table). The study also included participants with neuropathy in their hands/arms, retinopathy,

and color-blindness (whether actually color-blind or color-blind induced by wearing Variantor glasses (validation study participant conditions table). All materials used in the study were the final to-be-marketed version; however, no drug was used in the simulated dosing.

Summative Validation Study Enrollment

	User Group 1: Diabetes patients currently on Insulin	**User Group 2: Diabetes patients currently on oral medication only**	**User Group 3: HCPs who currently work with diabetes patients**	**TOTAL**
Orientation by CDE	N=15	N=15	N=15	N=45
Untrained	N=15	N=15	N=15	N=45
TOTAL	**N=30**	**N=30**	**N=30**	**N=90**

Summative Validation Study Dosing Administration

Study Session 1		**Study Session 2 (4 to 24 Hours After Session 1)**	
Group 1: Orientation by CDE or Group 2: Un-Trained (Supplied IFU)	Unaided Simulated Dosing Administration #1	Unaided Simulated Dosing Administration #2	Unaided Simulated Dosing Administration #3
	Context: Cartridges already at room temperature.	**Context:** Cartridges stored in refrigerator.	**Context:** Loose cartridges stored in a blood glucose meter kit.

Summative Validation Study Participant Conditions

Factor	**Number of Participants**
Color-Blind	N= 15 (25%)
Retinopathy	N= 35 (58%)
Neuropathy	N= 21 (35%)

Based on the FDA's feedback the study also included 2 conversion tasks:

1) After the first unaided dose, users were asked to perform a dose conversion from AFREZZA to injected mealtime insulin using that dose.
2) After the third unaided dose, users were asked to perform a dose conversion from injected mealtime insulin to AFREZZA.

Validation Results – Simulated Dose Administrations

This study included 270 unaided simulated dose administrations. Across all participant dosing simulations, 99% (267/270) were error free. The 3 errors involved improper cartridge selection by 3 different participants; 1 occurred in the trained user group and 2 occurred in the untrained user group. A close call was observed when a fourth untrained participant came close to not keeping the inhaler level. Of the 3 participants that committed an error, no errors were repeated and no pattern of use error could be attributed to the TI Inhalation System design.

In addition, after performing all 3 dose tasks, 100% (90/90) of participants stated they could safely use the device on a daily basis.

Validation Results – Dose Conversion

All 90 participants performed the dose conversion tasks successfully for both conversion of injected mealtime insulin to AFREZZA (90/90) and conversion of AFREZZA to injected mealtime insulin (90/90). This demonstrates the effectiveness of the dose conversion tables located in the IFU. Additionally, all participants stated they had no difficulty with dose conversion and no difficulty understanding the dose conversion tables.

Validation Results – Knowledge Probe (Storage and Care)

All 90 participants correctly answered all knowledge probes (540/540) related to proper storing and caring for the inhaler and cartridges. The participants correctly answered knowledge probes related to:

- Proper inhaler replacement time
- Proper cartridge storage conditions
- Proper foil pack storage location
- Proper wait time for a cartridge to reach room temperature
- Proper expiration date of a unopened foil pack
- And, proper expiration date of an opened blister strip

Although all participants were able to correctly answer all of the knowledge probe questions, one untrained participant had a close call when asked where to store a sealed foil package. The participant initially answered with where he would store the cartridges, not where the instructions or labeling recommend they should be stored. When the nature of the question

was clarified, the participant stated the correct answer of storing foil packages in the refrigerator.

Validation Results – IFU

The IFU provided adequate instruction to both trained and untrained participants for safe and effective use of the TI Inhalation System. Participants appreciated the design of the IFU indicating it was adequate in size for ease of reading, colorful, and easy to read/follow steps. All 90 participants stated they had no difficulty comprehending the IFU and assessed the content as complete and thorough. In addition, participants rated the ease of reading the IFU as "Very Easy" (mean=4.85 on a 5-point scale). Notably, 43 out of 45 untrained participants were able to self-educate using the IFU, labeling, and system and committed no errors. Across all participants, no errors were associated with the content or layout of the IFU as evidenced through debriefing responses in post-test interviews. Additionally, participants with retinopathy and colorblindness (or simulated colorblindness) had no difficulty using the IFU.

Validation Results – Package Labeling

The package labeling was effective across all participants including participants with color-blindness and retinopathy. There were no failures attributed to a labeling deficiency. The study evaluated the design and content of the carton, foil package, blister strip, and inhaler labeling. All 90 participants were able to read the message printed on top of the inhaler (Replace After 15 Days Use). All 90 participants stated they had no difficulty identifying and differentiating the cartridges and contents of the cartons, foil packages, and blister strips. All 90 participants stated the blister strip label provides clear indication there are either three 3-unit cartridges or three 6-unit cartridges contained within the strip. Although one participant did get confused and made an error, the participant became self-aware after looking at the dosing chart. There were no patterns of confusion, failure, or errors.

Subjective feedback collected throughout the study indicated that participants with diabetes and healthcare providers view AFREZZA favorably and are eager for market availability. Additionally, subjects saw value in using AFREZZA to inhale insulin over injecting insulin.

SUMMARY

Based on the results of the study, the TI Inhalation System (AFREZZA®) can be correctly, safely and effectively used by the intended user audiences (adults with type 1 or type 2 diabetes and HCPs). The device, packaging, labeling and associated instructions for use are validated and do not lead to any patterns of confusion, failures, errors, or patient safety risks.

Appendix 3 Brief Tabular Summaries of Completed TI Trials

This Appendix contains 3 tables that, together, include all completed TI Trials.

- Overview of Key Clinical Pharmacology Trials in the Technosphere Insulin Clinical Development Program
- Overview of Key Phase 2 and Phase 3 Trials in the Technosphere Insulin Clinical Development Program
- Other Completed Trials in the Technosphere Insulin Clinical Development Program

Note: The 2 ongoing trials (Trials 134 and 139) are not included in these tables.

Overview of Key Clinical Pharmacology Trials in the Technosphere Insulin Clinical Development Program

Trial	Trial Objectives	Treatment Administered	Inhaler	
			MedTone	Gen2
Healthy Subjects				
PDC-INS-0001[a]	PK/PD, TI vs sc insulin vs IV	TI: 100 U (BI Handihaler device) Insulin (sc): 10 IU Insulin (iv): 5 IU	NA	NA
PDC-INS-0001A[a]	BA,TI vs sc RHI	TI: 25 U RHI: 10 IU	X	
PDC-INS-0002[a]	BA, TI vs sc Insulin	TI: 25 U, 50 U, 100 U Insulin: 10 IU	X	
PDC-INS-0007[a]	PK/PD, TI radiolabeled	TI: 10 U	X	
MKC-TI-122[a]	PK of insulin & FDKP in lungs (BAL trial)	TI: 60 U	X	
MKC-T-140[b]	BA, FDKP, Gen2A vs MedTone, Effect of inspiratory effort and inhalation time	FDKP; Gen2A: 10 mg, 15 mg (single doses); MedTone (Model C): 10 mg (single dose)	X	X
MKC-TI-141[b]	BA of TI, Gen2B vs MedTone	Gen2B: 10 U, 20 U, 22 U MedTone: 15 U, 30 U	X	X
MKC-TI-142[b]	BA/BE, TI (MedTone vs Gen2)	Gen2: 2x 10 U or 1x 20 U; MedTone (Model C): 30 U	X	X
MKC-TI-176[c]	PK/PD, TI vs sc RHI	TI: 10 U, 20 U, 30 U, 60 U, and 80 U RHI: 15 IU		X
Mass Balance and Metabolite Profiling in Healthy Subjects				
MKC-T-123[a]	PK, ^{14}[C]- FDKP (IV vs PO)	IV: 10 mL [^{14}C] FDKP solution Oral: 100 mL [^{14}C] FDKP solution	NA	NA
DDI Trial with Bronchodilator and Inhaled Corticosteroid in Healthy Subjects				
MKC-TI-114[a]	DDI – effect of albuterol + fluticasone on PK of TI	TI: 45 U Albuterol: 180 µg Fluticasone: 440 µg	X	
Thorough QT_c Trial in Healthy Subjects				
MKC-T-131[a]	QTc Interval (effect of FDKP)	TI placebo: Supratherapeutic – 40 mg; Therapeutic – 20 mg Active control: 400 mg oral moxifloxacin Placebo control: empty cartridge	X	

Overview of Key Clinical Pharmacology Trials in the Technosphere Insulin Clinical Development Program

Trial	Trial Objectives	Treatment Administered	Inhaler	
			MedTone	Gen2
T1DM				
PDC-INS-0011[a]	BG control before or after hypercaloric meal	TI: 6 U, 12 U, 24 U	X	
MKC-TI-025[a]	PK/PD, TI vs sc RHI	TI: 30 U RHI: 10 IU	X	
MKC-TI-110[a]	BA, BE, TI vs sc RHI	TI: 30 U, 60 U RHI: 10 IU	X	
MKC-TI-116[a]	BE, TI A vs TI B vs sc RAA	TI: 2 x 15 U or 1 x 30 U RAA (insulin lispro): 10 IU	X	
MKC-TI-138[a]	BA/BE, TI MedTone Model C vs Model D	TI 30 U	X	
MKC-TI-177[c]	PK/PD, TI vs sc RAA	TI: 20 U RAA (insulin lispro): 8 U		X
T2DM				
PDC-INS-0003[a]	PK/PD, TI vs sc RHI	TI: 100 U RHI: 15 IU	X	
PDC-INS-0003A[a]	PK/PD, TI vs sc RHI	TI: 48 U RHI: 15 IU	X	
MKC-TI-03B[a]	PK/PD, prandial TI vs sc Insulin	TI 12 U, 24 U, 36 U, 48 U RHI: 0.15 IU/kg	X	
MKC-TI-003B2[a]	PK/PD, TI vs sc RHI	TI: 48 U, prandial RHI: 100 IU	X	
PDC-INS-0004A[a]	PK/PD, TI on BG control	TI: 12 U, 24 U, or 48 U, prandial	X	
MKC-TI-118[a,b]	Suppression of EGP, PK/PD – TI, insulin lispro, Exubera	TI: 45 U, 60 U, or 90 U Insulin lispro: 10 IU, 12 IU	X	
T2DM and Renal Impairment				
MKC-T-017[a]	PK, FDKP in DM + mild or moderate nephropathy vs DM normal kidney function	TI placebo: 20 mg (2 cartridges, 10 mg each)	X	
T2DM and Hepatic Impairment				
MKC-T-111[a]	PK, FDKP	TI placebo: 20 mg (2 cartridges of 10 mg/each)	X	

Overview of Key Clinical Pharmacology Trials in the Technosphere Insulin Clinical Development Program

Trial	Trial Objectives	Treatment Administered	Inhaler	
			MedTone	Gen2
T1DM or T2DM with URI				
MKC-TI-112[a]	PK of TI with URI and post recovery	TI: 5 mg (15 U), 10 mg (30 U)	X	
T2DM and Smoking				
MKC-TI-016[a]	Extrinsic factor-PK, TI in smokers vs nonsmokers	TI: 30 U, prandial	X	
Nondiabetic Subjects and Asthma				
MKC-TI-113[a]	PK of TI +/- salbuterol and/or after MCT in subjects with or without asthma	TI: 45 U Salbutamol: 200 µg Methacholine chloride	X	
T2DM and Asthma				
MKC-TI-027[a]	PK/PD, TI 7-day dosing in asthmatics vs non-asthmatics	TI: 15 U to 90 U	X	
Nondiabetic Subjects and COPD				
MKC-TI-015[a]	PK, TI in COPD vs no COPD	TI: 30 U	X	

BA=bioavailability; BE=bioequivalence; BG=blood glucose; CLD=chronic lung disease; C_{max}=maximum concentration of drug in plasma; COPD=chronic obstructive pulmonary disease; EGP=endogenous glucose production; GIR=glucose infusion rate; FDKP=fumaryl diketopiperazine; IU=international units; IV=intravenous; MCT=methacholine challenge test; NDA=New Drug Application; PD=pharmacodynamics; PK=pharmacokinetics PPG=postprandial glucose; PO=oral; RAA=rapid-acting analogue (of insulin); RHI=regular human insulin; sc=subcutaneous; TI=Technosphere Insulin; TI placebo = Technosphere particles (placebo, no insulin); U=units; URI=upper respiratory infection.
a = Trial was included in 2009 Original NDA.
b = Trial was included in 2010 Amendment.
c = Trial was included in 2013 Resubmission.

Overview of Key Phase 2 and Phase 3 Trials in the Technosphere Insulin Clinical Development Program					
Trial #	**Trial Design**	**Treatment Duration**	**Treatment Regimens**	**Inhaler Type**	**Submission**
Phase 3 Efficacy and Safety Trials					
MKC-TI-171 (T1DM)	prospective, open-label, multi-center, randomized, controlled, forced titration, trial	24 weeks	Forced titration/treat-to-target with individualized doses of: TI Gen2, TI MedTone, or RAA (insulin aspart)	MedTone and Gen2	2013
MKC-TI-009 (T1DM)	prospective, multicountry, multicenter, open-label, randomized, controlled trial comparing basal insulin and prandial TI vs basal insulin and RAA	52 weeks	TI: 15 to 90 U per meal plus basal insulin glargine RAA: insulin aspart 3 to 4 times per day plus basal insulin glargine	MedTone	2009
MKC-TI-117 (T1DM)	randomized, multicenter, open-label trial comparing the efficacy and safety of TI plus basal insulin vs RAA insulin lispro plus basal insulin	16 weeks	TI: 15 to 90 U of TI per meal plus basal insulin glargine RAA: insulin lispro plus basal insulin glargine	MedTone	2010
MKC-TI-175 (T2DM)	prospective, open-label, multi-center, randomized, controlled, forced titration, clinical trial	24 weeks	Forced titration/treat-to-target with individualized doses of: TI (plus OADs) or TP (plus OADs)	Gen2	2013
MKC-TI-102 (T2DM)	prospective multicenter, open-label, randomized, controlled comparison of basal insulin plus TI versus subcutaneous premixed insulin therapy	52 weeks	TI: 15 to 90 U of TI per meal plus basal insulin glargine Comparator: premixed insulin (BPR 70/30)	MedTone	2009
MKC-TI-014 (T2DM)	randomized, open-label trial with a run-in period (everyone: basal insulin glargine and prandial insulin aspart) followed by a randomized treatment period (TI or comparator)	24 weeks	Basal insulin plus either prandial TI (titrate as needed from 15 to 60 U per meal [dose was capped with an upper limit]) or prandial RAA insulin aspart (titrate as needed)	MedTone	2009

Overview of Key Phase 2 and Phase 3 Trials in the Technosphere Insulin Clinical Development Program					
Trial #	**Trial Design**	**Treatment Duration**	**Treatment Regimens**	**Inhaler Type**	**Submission**
Phase 3 Safety Trials					
MKC-TI-105 (T1DM and T2DM)	Pulmonary function safety trial in diabetic subjects (T1DM or T2DM) with asthma.	12 months	Usual care vs TI added to modified usual care	MedTone	2009
MKC-TI-030 (T1DM and T2DM)	pulmonary outcomes trial	2 years	TI: adjusted in increments of 15 U, as needed, up to a maximum of 90 U per meal. Comparator: usual antidiabetic care	MedTone	2009
MKC-TI-126 (T1DM and T2DM)	pulmonary function follow-up for subjects who completed Trials MKC-TI-009, MKC-TI-102, MKC-TI-103, or MKC-TI-030	2 months	Off treatment follow-up	MedTone in the parent trials	2009
MKC-TI-164 (T2DM)	Pulmonary function follow-up for subjects who completed Trial MKC-TI-162	27 weeks	Continued with treatment from MKC-TI-162	Gen2	2013
Phase 3 Supportive Efficacy and Safety Trials					
MKC-TI-162 (T2DM)	prospective, multicenter, open-label, randomized, forced-titration, clinical trial evaluating the efficacy and safety of TI in combination with basal insulin vs RAA plus basal insulin	16 weeks	TI: Individualized doses of TI plus insulin glargine RAA: insulin aspart plus insulin glargine	Gen2	2013
MKC-TI-103 (T2DM)	multicenter, open-label, randomized, controlled trial comparing prandial TI alone, combination of metformin and a secretagogue (sulfonylurea or meglitinide), or prandial TI + metformin Metformin doses ≥1000 mg/day (or at maximum tolerated dose) Secretagogue doses ≥0.5 the manufacturer-recommended daily dose (or at maximum tolerated dose)	24 weeks (12 weeks of randomized treatment followed by a 12-week observational period)	TI alone: 15 to 90 U of TI per meal; TI + Metformin: 15 to 90 U of TI per meal plus metformin (see trial design column) Metformin + Secretagogue: see trial design column for doses	MedTone	2009

Overview of Key Phase 2 and Phase 3 Trials in the Technosphere Insulin Clinical Development Program					
Trial #	**Trial Design**	**Treatment Duration**	**Treatment Regimens**	**Inhaler Type**	**Submission**
Phase 2 Supportive Trials					
MKC-TI-101 (T1DM)	randomized, multisite, open-label, sc prandial insulin substitution trial	12 weeks	Individualized TI doses based on prior sc prandial insulin dose	MedTone	2009
PDC-INS-0008 (T2DM)	multicenter, double-blind, randomized, placebo-controlled, parallel-group trial with meal challenge tests	12 weeks	Background OADs plus either TI (individualized dose) or TP	MedTone	2009
MKC-TI-026 (T2DM)	prospective, controlled, open-label, randomized, safety, and efficacy trial	12 weeks	TI: 15 to 60 U per meal Comparator: Standard of care	MedTone	2009
MKC-TI-005 (T2DM)	prospective, randomized, multicenter, double-blind, placebo-controlled, stepwise titration trial	11 weeks	Basal insulin glargine plus TI (14, 28, 42, or 56 U per meal) or TP	MedTone	2009
MKC-TI-010 (T2DM)	Uncontrolled long-term safety trial in T2DM subjects who completed Trials PDC-INS-0008 or MKC-TI-005	Up to 4 years	Continued TI therapy from parent trials	MedTone	2009

BG=blood glucose; OAD=oral anti-diabetic drugs; PD=pharmacodynamics; PPG=post-prandial glucose; RAA=rapid-acting analogue (of insulin); sc=subcutaneous; T1DM=type 1 diabetes mellitus; T2DM=type 2 diabetes mellitus; TI=Technosphere Insulin; TP=Technosphere particles (placebo, no insulin); U=units (fill content of TI cartridges).

Other Completed Trials in the Technosphere Insulin Clinical Development Program

Trial Number	Trial Title
MKC-129	A Trial for Determination of Inspiratory Flow Rates Using the Medtone® Inhaler and An Empty Cartridge in Subjects with Type 1 and Type 2 Diabetes
MKC-TI-104	A Phase 2, Open Label, Single-Center Trial of the use of Technosphere® Insulin as Prandial Insulin in Combination with Continuous Subcutaneous Insulin Infusion for Basal Insulin Requirements in Subjects with Type 1 Diabetes Mellitus
PDC-INS-0001B	Pharmacokinetics and Efficacy of Different Pulmonary Technosphere™/Insulin Formulations in Patients with Type 1 Diabetes
PDC-INS-001C	Inhalation of Technosphere™/Insulin: Effect of Varying the Insulin Loading of Technosphere™ on Insulin Bioavailability in Patients with Type 1 Diabetes
PDC-INS-002A	Dose Response Effects of Inhaled Technosphere™/Insulin vs. Subcutaneous Injection of Regular Human Insulin in Healthy Subjects
PDC-INS-0004	Supplementation of the Early Phase Insulin Release with Inhaled Technosphere™/Insulin in Comparison to Insulin Lispro and Regular Human Insulin in Patients with Type 2 Diabetes
PDC-INS-0006	Effect of Postprandially Inhaled Technosphere™/Insulin on Postprandial blood Glucose Levels in Patients with Type 2 Diabetes
MKC-143	Inspiratory Capacity and Handling Trial Using the Gen2C and MedTone® Inhaler Model D Delivery Systems in a Healthy Pediatric Population
MKC-TI-159	A Phase 2, Multicenter, Open-label, Single-arm Clinical Trial in Subjects with Type 1 or Type 2 Diabetes to Provide In-use Handling Data for the Gen 2 Inhaler
MKC-TI-147	A Phase 1, Single-center, Open-label, 2-part, Randomized, Crossover Clinical Trial in Healthy Normal Volunteers and Subjects with Type 2 Diabetes to Evaluate the Bioavailability and Dose Proportionality of Different Technosphere® Insulin Inhalation Powder Formulations (3 U, 4 U, and 6 U of Insulin per milligram of TI Inhalation Powder) Using a Gen2 Inhaler

Other Completed Trials in the Technosphere Insulin Clinical Development Program

MKC-TI-167	A Phase 1, Single-center, Open-label, Randomized, Crossover Design Clinical Trial in Healthy Normal Volunteers to Evaluate Insulin Exposure and Dose-proportionality Following Inhalation of Technosphere® Insulin Inhalation Powder (3 U and 4 U insulin/mg) using the Gen2 inhaler
MKC-TI-119	A Phase 2, Single-Center, Open-Label, Pharmacodynamic Clinical Trial to Evaluate the Effect of Technosphere® Insulin Inhalation Powder on Postprandial Glucose Levels in Subjects with Type 1 and Type 2 Diabetes Mellitus Ingesting Meals with Varied Carbohydrate Content
MKC-TI-158	A Single-center, Open-label, Crossover, Pilot Extension of Clinical Trial MKC-TI-119 to Evaluate the Effect of Frequent Self-monitoring of Blood Glucose Versus As Needed Self-monitoring of Blood Glucose on the Efficacy and Safety of Technosphere® Insulin Inhalation Powder in Subjects with Type 2 Diabetes Mellitus

Appendix 4 Euglycemic Clamp Technique

Reduction in blood glucose (BG) concentration by insulin is quantified through euglycemic clamp assessments in which glucose and low-dose insulin are infused to suppress endogenous insulin secretion and hepatic glucose release, and to stabilize BG concentrations. The test article is then administered and glucose is infused at a variable rate to maintain a constant BG.

Several TI clinical pharmacology trials utilized euglycemic clamp technique to characterize TI pharmacodynamics versus comparator insulins. At dosing, time 0, the subjects were administered the insulin study drugs (TI, sc RHI, or sc RAA) and a euglycemic clamp was continued for 8 hours post-dose. The appropriate adjustments of the glucose infusion rate (GIR) to maintain a glucose concentration of 90 ± 10 mg/dl was automatically calculated (Biostator). When a GIR that exceeded the Biostator's capability was necessary, a secondary glucose infusion was provide by an external pump (Infusion Pump Midpress TE 171 CW3, Terumo Corporation, Tokyo, Japan). The GIR required to keep a constant blood glucose level during the 8-hour test period was recorded per minute. The GIR provided by the external pump was added to the GIR provided by the Biostator as necessary.

The GIR represents the instantaneous demand for glucose and the area under the GIR-time curve (GIR AUC) represents the total glucose demand. If the BG concentration remains constant, the GIR matches the rate of glucose disposal induced by the test article insulin. There is a lag between the rise in insulin concentration and the rise in GIR such that GIR tmax always occurs after insulin tmax and GIR persists after insulin concentration returns to baseline. The glucose disposal rate increases with insulin concentration but saturates (reaches a maximum [Emax]) at high insulin concentrations.

Appendix 5 Brief Summaries of Key Phase 3 Efficacy Trials

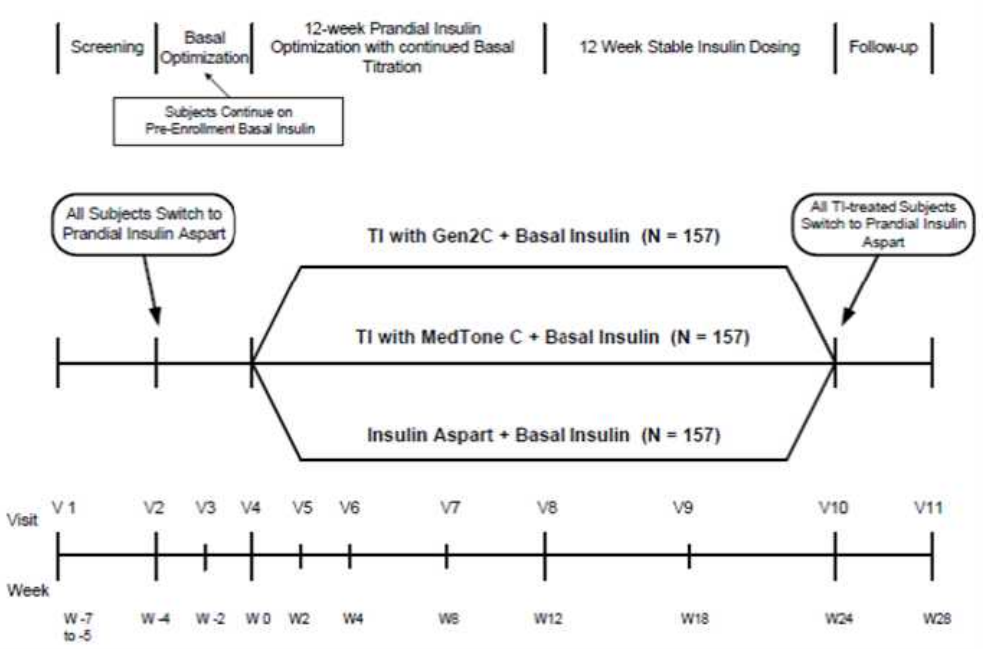
This Appendix contains brief summaries of the following trials:

- MKC-TI-171, MKC-TI-009, and MKC-TI-117 in subjects with type 1 diabetes mellitus
- MKC-TI-175, MKC-TI-102, and MKC-TI-014 in subjects with type 2 diabetes mellitus

Trial MKC-TI-171 (Brazil, Russia, Ukraine, and United States)

Population: T1DM, BMI ≤38 kg/m^2, HbA1c ≥7.5% and ≤10.0%, FEV_1 ≥70% NHANES III predicted; FVC ≥70% NHANES III predicted; and FEV_1/FVC ≥ NHANES III lower limit of normal (LLN)

Design: open-label, randomized, controlled, forced-titration, treat-to-target trial



Treatment groups: prandial insulin (T1 Gen2, TI MedTone [safety only], or insulin aspart) added to a basal insulin

Treatment duration: 24 weeks

Primary endpoint: Change in HbA1c (%) from baseline (end of run-in period) to end of treatment (Week 24) in the TI Gen2 group vs the insulin aspart group

Key secondary endpoints:

- Change from baseline to Week 24 for FPG, 7-point glucose profile, and body weight
- Proportion of subjects achieving pre-specified HbA1c targets

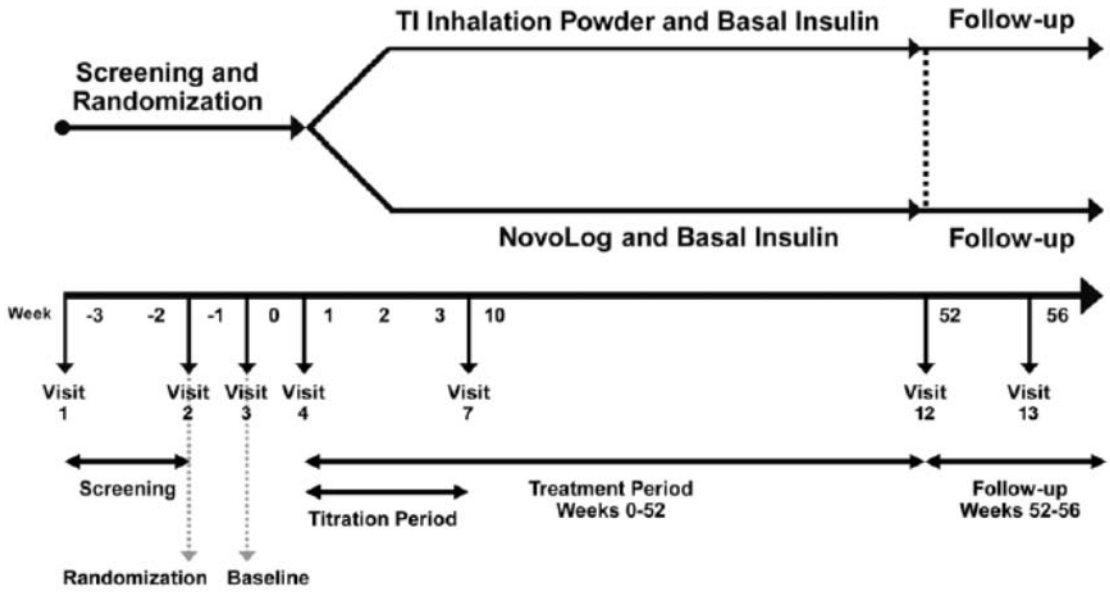
Results:

TI Gen2 plus basal insulin was noninferior to insulin aspart plus basal insulin with regard to HbA1c improvement over 24 weeks of treatment. Additionally, prandial TI Gen2 with basal insulin resulted in lower FPG values, reduced risk of hypoglycemia, and less weight gain (weight neutrality) compared with the insulin aspart regimen. The overall safety profiles were similar regardless of the inhaler used to administer TI.

Trial MKC-TI-009 (Argentina, Brazil, Canada, Chile, Mexico, Poland, the Russian Federation Spain, United Kingdom, and United States)

Population: T1DM, HbA1c > 7.0% and ≤ 11.0%, $FEV_1 \geq 70\%$ predicted; TLC ≥ 80% predicted; (DL_{CO}) (uncorrected) ≥ 70% predicted

Design: prospective, open-label, randomized, controlled trial



Treatment groups: basal insulin/prandial TI MedTone vs basal insulin/RAA insulin aspart

Treatment duration: 52 weeks

Primary endpoint: Change from baseline to Week 52 in HbA1c (%)

Key secondary endpoints:

- Change from baseline for blood glucose during a meal challenge, 7-point glucose profile, and weight.
- Proportion of subjects achieving pre-specified HbA1c and post-prandial glucose targets

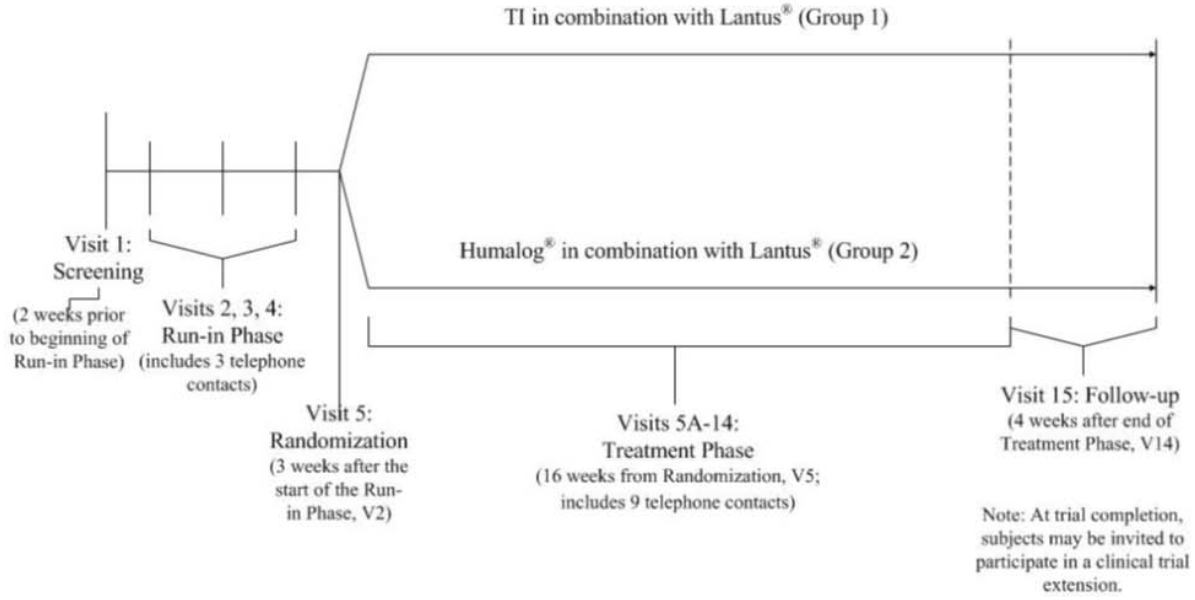
Results:

Noninferiority of TI + basal insulin with respect to insulin aspart + basal insulin in reducing HbA1c levels could not be confirmed because the between group difference was 0.24 (95% CI [0.08, 0.40]) in favor of insulin aspart + basal insulin with the upper bound missing the pre specified noninferiority criterion that this should be <0.40. However, TI + basal insulin treatment resulted in lower FPG and 1-hour PPG and less total hypoglycemia in the context of weight neutrality.

Trial MKC-TI-117 (Brazil and United States)

Population: T1DM (>12 months)**,** BMI ≤ 30 kg/m^2**,** HbA1c > 7.0% and ≤ 9.0%**,** FEV_1 ≥70% predicted, TLC ≥80% predicted, DLco (uncorrected) ≥70% predicted

Design: randomized, open-label trial



Treatment groups: basal insulin plus prandial insulin (TI MedTone or insulin lispro)

Treatment duration: 16 weeks

Primary endpoint: Change from baseline to Week 16 in HbA1c (%)

Key secondary endpoints:

- Change from baseline for 7-point glucose profile and weight.
- Proportion of subjects achieving pre-specified HbA1c targets
- Post-prandial glucose control expressed as glucose excursions during a standardized liquid meal challenge test

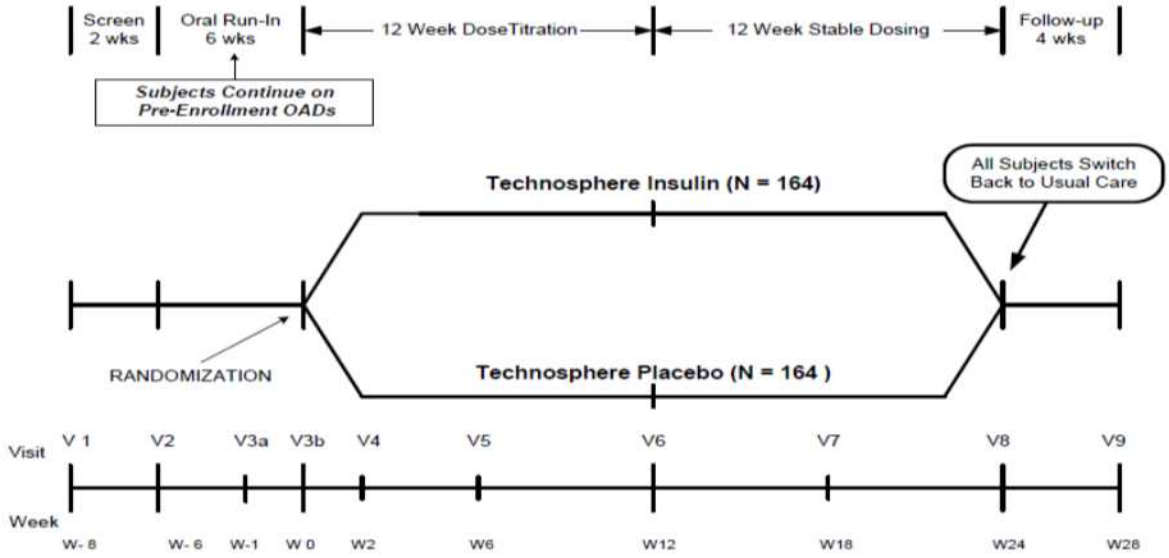
Results:

The original protocol-specified sample size was 230 subjects. However, because of the decision by MKC to focus development efforts on the Gen2 device and no longer support clinical trials with the MedTone device, this trial was prematurely terminated. Only 56% of required subjects had been recruited at the time of trial termination (65 subjects per treatment group). Despite the small sample size, a non-prespecified interim analysis noted that noninferiority for the primary efficacy endpoint was met: HbA1c change from baseline -0.10% for TI group, -0.03% for insulin lispro; mean treatment difference -0.07 (-0.31, 0.17). Fewer TI-treated subjects reported severe hypoglycemia events than those treated with insulin lispro (23% versus 35%).

Trial MKC-TI-175 (Brazil, Russia, Ukraine, and United States)

Population: T2DM (≥ 12 months)**,** BMI ≤45 kg/m^2, HbA1c ≥7.5% and ≤10.0%, insulin-naïve**,** FEV_1 ≥70% predicted; FVC ≥70% predicted; and FEV_1/FVC ≥ LLN

Design: double-blind, randomized, controlled, forced titration, treat-to-target trial



Treatment groups: OAD therapy plus either TI Gen2 or TP (Technosphere particles without insulin [placebo])

Trial duration: 24 weeks

Primary endpoint: Change from baseline to Week 24 in HbA1c (%)

Key secondary endpoints:

- Change from baseline to Week 24 for FPG, post-prandial glucose, 7-point glucose profile, and body weight
- Proportion of subjects achieving pre-specified HbA1c targets

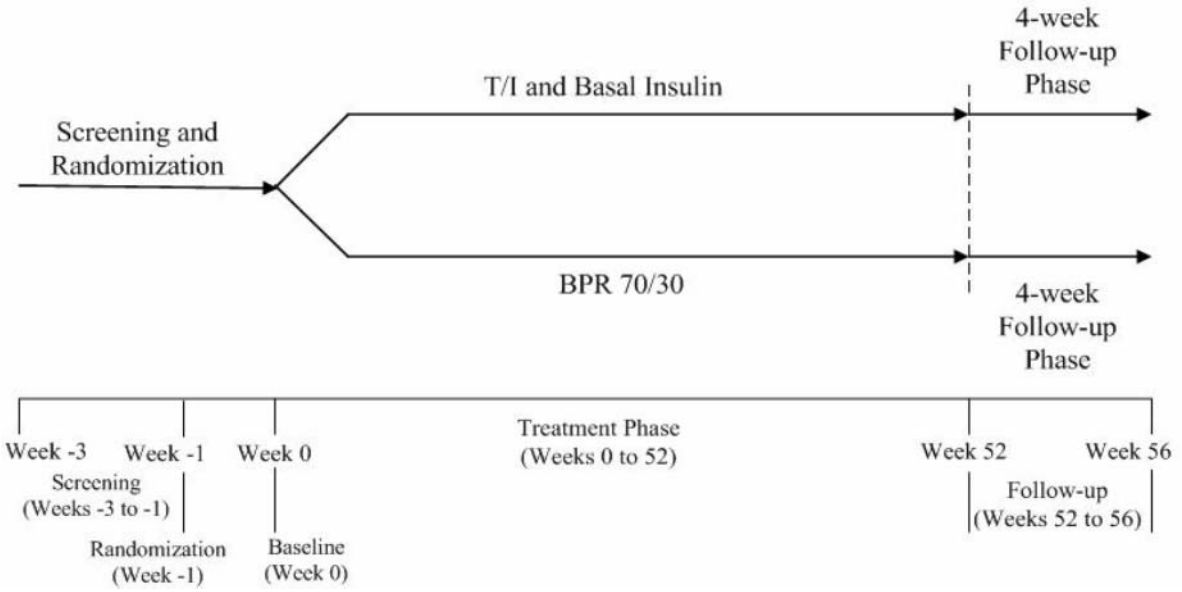
Results:

TI Gen2 therapy, when added to one or more OADs in type 2 diabetic patients with inadequate glycemic control on OAD therapy alone, results in superior HbA1c reduction, target HbA1c attainment, clinically meaningful decreases in postprandial blood glucose excursions, and minimal weight gain compared with placebo. TI Gen2 was well-tolerated and no new safety signals were detected. As expected, a higher incidence of hypoglycemia in the TI group compared with placebo was noted, but there was no significant difference in the incidence of severe hypoglycemia between the treatment groups.

Trial MKC-TI-102 (United States, Canada, Chile, Argentina, the Russian Federation, Brazil, Mexico, Spain, Poland, and United Kingdom)

Population: T2DM**,** HbA1c > 7.0% and ≤ 11.0%

Design: open-label, randomized, controlled trial



Treatment groups: prandial TI plus basal insulin vs premixed insulin (BPR 70/30)

Treatment duration: 52-weeks with a 4-week follow-up period

Primary endpoint: Change from baseline to Week 52 in HbA1c (%)

Key secondary endpoints:

- Change from baseline for blood glucose during a meal challenge, 7-point glucose profile, and weight.
- Proportion of subjects achieving pre-specified HbA1c and post-prandial glucose targets

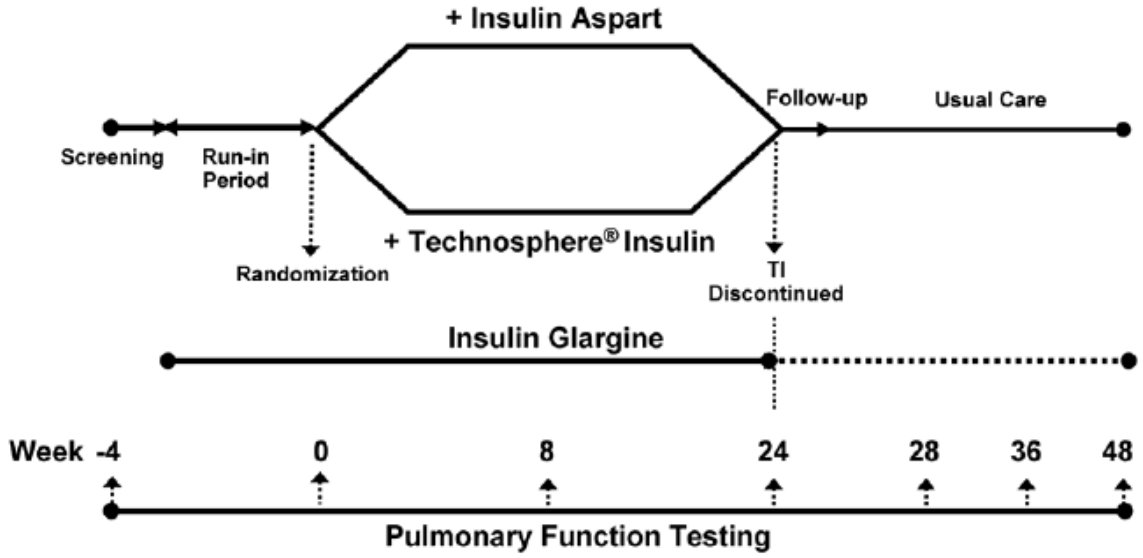
Results:

TI + basal insulin was noninferior to BPR 70/30 in terms of the primary assessment of HbA1c change at 52 weeks. TI + basal insulin, like BPR 70/30, provided a significant reduction in HbA1c that was sustained over 52 weeks. TI + basal insulin resulted in less weight gain. The 7-point blood glucose measurements indicated that postprandial glycemic excursions were of lesser magnitude with TI + basal insulin than with BPR 70/30. There were more hypoglycemic events in the BPR 70/30 group than in the TI group.

Trial MKC-TI-014 (Russian Federation)

Population: T2DM**,** HbA1c ≥7.0 % and ≤11.5 %**,** FVC and FEV_1 ≥70 % and ≤125% of predicted

Design: randomized, open-label trial



Treatment groups: basal insulin plus prandial insulin (TI or insulin aspart)

Trial duration: 24 weeks

Primary endpoint: Change from baseline to Week 24 in HbA1c (%)

Results:

The mean HbA1c change from baseline over 24 weeks (-0.90% for TI-treated and -1.11% for insulin aspart-treated subjects in the per-protocol [PP] Population) was clinically meaningful in both treatment groups but the upper margin of the 90% CI (0.41) of the between group difference exceeded the pre-specified equivalence margin of 0.40 and thus failed to meet the protocol-specified primary endpoint. The 90% CI of treatment difference was (-0.05, 0.35) for the mITT population and the treatment differences between TI and insulin aspart were small for both analysis populations (0.21% and 0.15% for the PP and mITT populations, respectively).

Appendix 6 Serious TEAEs Related to Hypoglycemia During Treatment

T1DM (MKC-TI-171)

Site Number/ Subject Number/ Sex/Age/Race[a]	Serious Event: Preferred Term (Verbatim Term)	Start Date of Event	End Date of Event	Severity	Relationship to Trial Drug	Outcome
TI Gen2						
004/2116 F/46/W	Hypoglycaemic Unconsciousness (Hypoglycemia with loss of consciousness)	2012-10-24	2012-10-24	Severe	Related	Resolved
129/1743 F/54/W	Hypoglycaemia (Severe Hypoglycemia)	2012-08-02	2012-08-02	Severe	Possibly	Resolved
	Hypoglycaemia (Severe Hypoglycemia)	2012-09-02	2012-09-02	Severe	Related	Resolved
	Hypoglycaemia (Severe Hypoglycemia)	2012-09-14	2012-09-14	Severe	Related	Resolved
	Hypoglycaemia (Severe Hypoglycemia)	2012-09-15	2012-09-15	Severe	Related	Resolved
	Hypoglycaemia (Severe Hypoglycemia)	2012-10-01	2012-10-01	Severe	Related	Resolved
553/2000 M/38/W	Hypoglycaemic Seizure (hypoglycemia with convulsions)	2012-12-08	2012-12-08	Severe	Possibly	Resolved

T1DM (MKC-TI-171)

Site Number/ Subject Number/ Sex/Age/Race[a]	Serious Event: Preferred Term (Verbatim Term)	Start Date of Event	End Date of Event	Severity	Relationship to Trial Drug	Outcome
TI MedTone						
272/1940 M/54/W	Hypoglycaemic Unconsciousness (Hypoglycemia with loss of Consciousness)	2013-03-05	2013-03-05	Severe	Unrelated	Resolved
384/2148 F/67/W	Hypoglycaemic Unconsciousness (Hypoglycemia with loss of Consciousness)	2012-12-21	2012-12-21	Severe	Possibly	Resolved
	Hypoglycaemic Unconsciousness (Hypoglycemia with loss of Consciousness)	2013-01-08	2013-01-08	Severe	Possibly	Resolved
483/2296 M/42/W	Hypoglycaemic Unconsciousness (Hypoglycemia with loss of Consciousness)	2013-02-18	2013-02-18	Severe	Possibly	Resolved
505/5378 M/36/W	Hypoglycaemic Seizure (Hypoglycemic seizure)	2012-07-21	2012-07-21	Moderate	Related	Resolved
663/1897 M/51/W	Hypoglycaemic Unconsciousness (Hypoglycemia with loss of Consciousness)	2012-12-20	2012-12-20	Severe	Related	Resolved
679/1167 M/76/W	Hypoglycaemia (severe hypoglycemia event)	2012-05-24	2012-05-24	Severe	Related	Resolved
876/1759 M/55/W	Hypoglycaemia (severe hypoglycaemia with mental confusion	2012-08-10	2012-08-10	Moderate	Unrelated	Resolved

T1DM (MKC-TI-171)

Site Number/ Subject Number/ Sex/Age/Race[a]	Serious Event: Preferred Term (Verbatim Term)	Start Date of Event	End Date of Event	Severity	Relationship to Trial Drug	Outcome
Comparator (Insulin Aspart)						
017/1601 F/42/W	Hypoglycaemic Seizure (Hypoglycemic seizure)	2012-08-13	2012-08-13	Severe	Related	Resolved
026/5372 F/46/W	Hypoglycaemia (Severe hypoglycemia)	2012-06-13	2012-06-13	Severe	Related	Resolved
141/2091 M/22/W	Hypoglycaemic Unconsciousness (Hypoglycemia with loss of Consciousness)	2013-04-13	2013-04-13	Severe	Unrelated	Resolved
210/5061 F/51/W	Hypoglycaemic Unconsciousness (Hypoglycemia with loss of Consciousness)	2012-04-20	2012-04-21	Severe	Related	Resolved

Abbreviations: A=Asian; B=black; F=female; M=male; T1DM=type 1 diabetes mellitus; TI=Technosphere Insulin; W=white.

Notes: Prandial insulin treatment phase and follow-up = period from randomization at Week 0 (Visit 4) through 30 days after last dose (inclusive).
Basal insulin trial treatments included insulin glargine, insulin detemir, and NPH insulin; prandial insulin trial treatments included TI Gen2, TI MedTone, and insulin aspart.

a: Age is age in years at trial entry.

Appendix 7 Dosing Instructions

The proposed marketed product is Technosphere Insulin (TI) Inhalation Powder delivered by the Gen2 inhaler.

TI should be administered immediately before starting a meal or within 20 minutes after starting a meal so that prandial glucose absorption is aligned with TI's rapid absorption/onset of action.

Due to TI's shorter duration of action compared with subcutaneously administered regular human insulin or rapid-acting analogues of insulin, some patients may benefit from taking a second (supplemental) dose of TI approximately 90 minutes after the meal if blood glucose remains elevated at this time.

To initiate therapy in insulin-naïve patients, a "3U" (labeled as containing the equivalent of 3 units of subcutaneous [sc] insulin) TI cartridge should be taken before each meal.

For patients transitioning from insulin regimens that include sc intermediate or longer-acting insulin, the starting TI dose should be 50% of the patient's total daily insulin dose divided among main meals. The remaining 50% of the patient's total daily insulin dose should be taken as the original sc insulin administered as prescribed.

To replace a sc prandial insulin with TI, the corresponding TI dose (in sc equivalents) should be used. For example, a patient currently taking 3 units of a sc prandial insulin should take a "3U" cartridge of TI at mealtime. For patients currently taking an intermediate dose (ie, not a multiple of 3) of sc insulin, the corresponding TI dose is rounded up such that a patient taking 4, 5, or 6 units of a sc prandial insulin should take a "6U" TI cartridge. Patients can use combinations of the "3U" and "6U" TI cartridges to achieve their dose.

For all patients, TI treatment needs to be individualized, and dose adjustment may be required based on the patient's need (e.g., blood glucose levels, meal size and composition, exercise habits). Glucose monitoring is recommended for all patients with diabetes, and each patient should be titrated to his/her optimal dosage based on blood glucose monitoring results. Titration to the appropriate TI dose is done by adjusting subsequent TI doses (for future meals) based on glucose levels taken 90 to 120 minutes following each meal.

Appendix 8 TEAEs Experienced by ≥2% of Subjects in T1DM and T2DM

T1DM: TEAEs Experienced by ≥2% of Subjects in Any Treatment Group (2013 Resubmission Safety Population)

Preferred Term	TI Total [N=1026] SYE=697 n (%)	Comparator [N=835] SYE=778 n (%)
Any TEAE	698 (68.0)	523 (62.6)
Any TEAE excluding cough	614 (59.8)	517 (61.9)
Upper respiratory tract infection	120 (11.7)	107 (12.8)
Nasopharyngitis	82 (8.0)	86 (10.3)
Headache	48 (4.7)	23 (2.8)
Influenza	48 (4.7)	51 (6.1)
Hypoglycemia	42 (4.1)	40 (4.8)
Oropharyngeal pain	36 (3.5)	14 (1.7)
Pulmonary function test decreased	29 (2.8)	8 (1.0)
Bronchitis	26 (2.5)	17 (2.0)
Urinary tract infection	24 (2.3)	16 (1.9)
Sinusitis	22 (2.1)	21 (2.5)
Throat irritation	21 (2.0)	2 (0.2)

Abbreviations: MedDRA= Medical Dictionary for Regulatory Activities; SYE=subject-year exposure; T1DM=type 1 diabetes mellitus; TEAE=treatment-emergent adverse event; TI = Technosphere Insulin.
.Note(s): Adverse events were coded using the MedDRA dictionary (Version 15.1).
Each subject is counted only once per system organ class and preferred term combined.

T2DM: TEAEs Experienced by ≥2% of Subjects in Any Treatment Group (2013 Resubmission Safety Population)

Preferred Term	TI Total [N=1991] SYE=1356 n (%)	TP Total [N=290] SYE=98 n (%)	Comparator [N=1363] SYE=1374 n (%)
Any TEAE	1260 (63.3)	153 (52.8)	814 (59.7)
Any TEAE excluding cough	1144 (57.5)	133 (45.9)	806 (59.1)
Upper respiratory tract infection	164 (8.2)	14 (4.8)	132 (9.7)
Nasopharyngitis	138 (6.9)	24 (8.3)	86 (6.3)
Bronchitis	64 (3.2)	10 (3.4)	41 (3.0)
Hypertension	63 (3.2)	3 (1.0)	57 (4.2)
Headache	61 (3.1)	8 (2.8)	24 (1.8)
Influenza	62 (3.1)	3 (1.0)	48 (3.5)
Diarrhea	53 (2.7)	4 (1.4)	30 (2.2)
Throat irritation	47 (2.4)	4 (1.4)	1 (0.1)
Productive cough	43 (2.2)	3 (1.0)	12 (0.9)
Oropharyngeal pain	41 (2.1)	8 (2.8)	11 (0.8)
Fatigue	40 (2.0)	2 (0.7)	8 (0.6)
Nausea	40 (2.0)	1 (0.3)	14 (1.0)
Back pain	37 (1.9)	5 (1.7)	28 (2.1)
Edema peripheral	38 (1.9)	0	29 (2.1)
Urinary tract infection	38 (1.9)	2 (0.7)	37 (2.7)
Sinusitis	33 (1.7)	3 (1.0)	28 (2.1)
Diabetic retinopathy	29 (1.5)	0	32 (2.3)

Abbreviations: MedDRA= Medical Dictionary for Regulatory Activities; SYE=subject-year exposure; T2DM=type 2 diabetes mellitus; TEAE=treatment-emergent adverse event; TI = Technosphere Insulin; TP=Technosphere particles (placebo, no insulin).
Note(s): Adverse events were coded using the MedDRA dictionary (Version 15.1).
Each subject is counted only once per system organ class and preferred term combined.

Appendix 9 Pulmonary Function Test Schedules

PFT Testing Schedule in Phase 2/3 Technosphere Insulin Trials

Trial	Trial Drug Treatment phase	Key PFT Inclusion Criteria	PFT schedule	Schedule of PFT after cessation of the trial drug
Type 1 Diabetes				
MKC-TI-101	12 weeks	FEV_1 = 70-125% predicted FVC = 70-125% predicted DLCo = 75-125% predicted	Week 4 (Baseline) Weeks 1, 8, 12	None
MKC-TI -009	52 weeks	FEV_1 ≥ 70% predicted DLCo ≥ 70% predicted TLC ≥ 80% predicted	Week 3 (Baseline) Week 14, 26, 38, 52	4 weeks
MKC-TI-117	16 weeks	FEV_1 ≥ 70% predicted FEV1/FVC >LLN DLCo ≥ 70% predicted TLC ≥ 80% predicted	Week -5 (Baseline) Week 16	4 weeks
MKC-TI-171	24 weeks	FEV_1 ≥ 70% predicted FVC ≥ 70% predicted FEV1/FVC >LLN	Week -3 (Screening) Week 4 (Baseline) Weeks 12, 24	4 weeks
Type 2 Diabetes				
MKC-TI-005	13 weeks	FEV_1 ≥ 75% predicted FVC ≥ 75% predicted DLCo ≥ 75% predicted	Week 1 (Baseline spirometry, DLCo) Week 6 (spirometry only) Week 13 (spirometry, DLCo)	None
PDC-INS-0008	12 weeks	FEV_1 = 80-120% predicted FVC = 80-120% predicted DLCo = 80-120 % predicted	Week 0 Screening Week 2 (Baseline) Weeks 6 (spirometry only) Week 10 (spirometry only) Week 14 (spirometry, DLco)	None
MKC-TI-026	12 weeks	FEV_1 = 70-125% predicted FVC = 70-125% predicted	Week 0 (Baseline) Week 14	None

PFT Testing Schedule in Phase 2/3 Technosphere Insulin Trials

Trial	Trial Drug Treatment phase	Key PFT Inclusion Criteria	PFT schedule	Schedule of PFT after cessation of the trial drug
MKC-TI-014	24 weeks	FEV_1 => 70-125% predicted FVC = >70-125% predicted	Week 4 (spirometry only) Week 0 (Baseline, (spirometry only) Weeks 8, 24 (spirometry only)	Weeks 4, 12, 24
MKC-TI-103	24 weeks	$FEV_1 \geq$ 70% predicted DLCo ≥ 70% predicted TLC ≥ 80% predicted	Week 2 (Baseline) Weeks 4, 12 Weeks 16, 24	4 weeks
MKC-TI-102	52 weeks	$FEV_1 \geq$ 70% predicted DLCo ≥ 70% predicted TLC ≥ 80% predicted	Week 3 (Baseline) Week 14, 26, 38, 52	4 weeks
MKC-TI-175	24 weeks	$FEV_1 \geq$ 70% predicted FVC ≥ 70% predicted FEV1/FVC >LLN	Week -3 (Screening) Week 6 (Baseline) Weeks 12, 24	4 weeks
Types 1 and 2 Diabetes				
MKC-TI-030	24 months	$FEV_1 \geq$ 70% predicted FVC ≥ 70% predicted DLCo ≥ 70% predicted TLC ≥ 80% predicted	Weeks 3 (Baseline) Weeks 12, 24, 52, 76, 104	None
Uncontrolled Trial				
MKC-TI-010	up to 48 months	Participation in MKC-TI-005 or PDC-INS-0008 trial	Week 0 (Baseline), then Spirometry every 24 weeks, DLco every 52 weeks	NA
Safety Follow-up Trial				
MKC-TI-126	NA	Participation in MKC-TI-009. 102, 103, or 030 trial	NA	4 and 12 Weeks

Appendix 10 Pulmonary Function Test Results

Mean Baseline, Mean Change from Baseline in Absolute and Adjusted Values, and Treatment Group Difference in LS Mean Change From Baseline in FEV_1 (L) by Visit, MMRM Model, T1DM and T2DM Combined (Pooled PFT Population)

	Absolute Values		MMRM Model		
Visit Statistics	**TI**	**Comparator**	**TI**	**Comparator**	**Treatment Difference TI - Comparator**
Baseline					
N	1532	1542			
Mean	3.20	3.21			
SD	0.762	0.806			
Month 3					
N	1173	1262	1173	1262	
Mean/LS Mean [a]	-0.07	-0.04	-0.08	-0.04	-0.040
SD/SE [a]	0.201	0.167	0.007	0.007	0.0079
95% CI			(-0.09, -0.07)	(-0.05, -0.03)	(-0.056,-0.025)
Month 6					
N	1058	1202	1058	1202	
Mean/LS Mean [a]	-0.10	-0.06	-0.11	-0.06	-0.043
SD/SE [a]	0.205	0.189	0.007	0.007	0.0080
95% CI			(-0.12, -0.09)	(-0.08, -0.05)	(-0.059,-0.028)
Month 9					
N	454	519	454	519	
Mean/LS Mean [a]	-0.10	-0.07	-0.11	-0.08	-0.036
SD/SE [a]	0.232	0.189	0.008	0.008	0.0102
95% CI			(-0.13, -0.10)	(-0.09, -0.06)	(-0.056,-0.016)
Month 12					
N	801	957	801	957	
Mean/LS Mean [a]	-0.10	-0.07	-0.11	-0.07	-0.038
SD/SE [a]	0.220	0.203	0.008	0.007	0.0089
95% CI			(-0.13, -0.10)	(-0.09, -0.06)	(-0.055,-0.020)
Month 18					
N	507	674	507	674	
Mean/LS Mean [a]	-0.13	-0.10	-0.14	-0.09	-0.045
SD/SE [a]	0.214	0.214	0.009	0.008	0.0104
95% CI			(-0.15, -0.12)	(-0.11, -0.08)	(-0.065,-0.025)
Month 24					
N	380	596	380	596	
Mean/LS Mean [a]	-0.16	-0.12	-0.16	-0.11	-0.045
SD/SE [a]	0.208	0.212	0.010	0.009	0.0118
95% CI			(-0.18, -0.14)	(-0.13, -0.10)	(-0.069,-0.022)

Abbreviations: CI=confidence interval; FEV_1=forced expiratory volume in one second; LS=least squares; MMRM=mixed model repeated measures; N=number of subjects; PFT=pulmonary function test; SD=standard deviation; SE=standard error; T1DM=type 1 diabetes mellitus; T2DM=type 2 diabetes mellitus; TI=Technosphere Insulin.
a: Mean and SD are for absolute values; LS Mean and SE are for adjusted values.
Mean values shown for baseline; mean changes from baseline shown for all other time points.
LS Mean, SE, adjusted mean difference, 95% CIs are derived from MMRM analysis with the terms of disease type, region, treatment, age, gender, height, visit, and baseline PFT measurement values in the model.
CS variance-covariance structure used.
Trials contributing to the pooled PFT population: MKC-TI-009, MKC-TI-030, and MKC-TI-102.

Appendix 11 List of the Cardiovascular Preferred Terms for Both the Broad and Custom Analyses

Cardiovascular Adverse Event Preferred Terms (Broad Analysis)	
MedDRA 7.1	***MedDRA 15.1***
Acute coronary syndrome	
Acute myocardial infarction	
Age indeterminate myocardial infarction	Myocardial infarction
Angina pectoris	
Angina unstable	
Angiopathy	
Aortic aneurysm	
Aortic atherosclerosis	Aortic arteriosclerosis
Aortic calcification	
Aortic stenosis	
Aortic valve incompetence	
Aortic valve sclerosis	
Aortic valve stenosis	
Arrhythmia	
Arterial disorder	
Arterial insufficiency	
Atherosclerosis	Arteriosclerosis
Atherosclerosis obliterans	Peripheral arterial occlusive disease
Atrial fibrillation	
Atrial flutter	
Atrioventricular block first degree	
Axillary pain	
Bifascicular block	
Bradycardia	
Bundle branch block left	
Bundle branch block right	
Cardiac aneurysm	
Cardiac arrest	
Cardiac discomfort	
Cardiac failure	
Cardiac failure acute	
Cardiac failure chronic	
Cardiac failure congestive	
Cardiac flutter	
Cardiac valve disease	
Cardiomegaly	

Cardiovascular Adverse Event Preferred Terms (Broad Analysis)	
MedDRA 7.1	***MedDRA 15.1***
Cardiomyopathy	
Chest pain	
Circulatory collapse	
Conduction disorder	
Coronary artery atherosclerosis	Arteriosclerosis coronary artery
Coronary artery disease	
Coronary artery insufficiency	
Coronary artery occlusion	
Coronary artery stenosis	
Deep vein thrombosis	
Diabetic macroangiopathy	
Diastolic dysfunction	
Essential hypertension	
Extrasystoles	
Extremity necrosis	
Flushing	
Haematoma	
Hot flush	
Hyperaemia	
Hypertension	
Hypertensive angiopathy	
Hypertensive cardiomyopathy	
Hypertensive crisis	
Hypertensive heart disease	
Hypotension	
Intermittent claudication	
Intracardiac thrombus	
Ischaemia	
Ischaemic cardiomyopathy	
Mitral valve incompetence	
Mitral valve prolapse	
Myocardial infarction	
Myocardial ischaemia	
Non-cardiac chest pain	
Orthostatic hypotension	
Pallor	
Palpitations	
Pericarditis	
Peripheral coldness	

Cardiovascular Adverse Event Preferred Terms (Broad Analysis)	
MedDRA 7.1	***MedDRA 15.1***
Peripheral vascular disorder	
Petechiae	
Phlebitis	
Phlebothrombosis	Venous thrombosis
Raynaud's phenomenon	
Sinus arrhythmia	
Sinus bradycardia	
Sinus tachycardia	
Sudden death	
Supraventricular extrasystoles	
Supraventricular tachycardia	
Tachycardia	
Thrombophlebitis	
Thrombophlebitis superficial	
Thrombosis	
Tricuspid valve incompetence	
Varicophlebitis	
Varicose vein	
Varicose vein operation	
Venous insufficiency	
Venous stasis	Venous insufficiency
Ventricular arrhythmia	
Ventricular extrasystoles	
Ventricular hypertrophy	
Ventricular tachycardia	

Abbreviation: MedDRA=Medical Dictionary for Regulatory Activities

Note: Blank in the MedDRA 15.1 column indicates no change in preferred term.

Cardiovascular Adverse Event Preferred Terms (Custom Analysis)	
MedDRA 7.1	***MedDRA 15.1***
Acute myocardial infarction	
Basilar artery thrombosis	
Brain stem infarction	
Brain stem stroke	
Brain stem thrombosis	
Carotid arterial embolus	
Carotid artery thrombosis	
Cerebellar infarction	
Cerebral artery embolism	
Cerebral artery thrombosis	
Cerebral infarction	
Cerebral thrombosis	
Cerebrovascular accident	
Coronary artery thrombosis	
Embolic cerebral infarction	
Embolic stroke	
Hemorrhagic cerebral infarction	Haemorrhagic cerebral infarction
Hemorrhagic stroke	Haemorrhagic stroke
Hemorrhagic transformation stroke	Haemorrhagic transformation stroke
Ischemic cerebral infarction	Ischaemic cerebral infarction
Ischemic stroke	Ischaemic stroke
Lacunar infarction	
Lateral medullary syndrome	
Moyamoya disease	
Myocardial infarction	
Papillary muscle infarction	
Postprocedural myocardial infarction	Post procedural myocardial infarction
Postprocedural stroke	Post procedural stroke
Silent myocardial infarction	
Stroke in evolution	
Thalamic infarction	
Thrombotic cerebral infarction	
Thrombotic stroke	
Wallenberg syndrome	

Abbreviation: MedDRA=Medical Dictionary for Regulatory Activities

Note: Blank in the MedDRA 15.1 column indicates no change in preferred term.

Appendix 12 List of Cerebrovascular Preferred Terms

Cerebrovascular Adverse Event Preferred Terms	
MedDRA 7.1	***MedDRA 15.1***
Carotid artery stenosis	
Cerebral atherosclerosis	Cerebral arteriosclerosis
Cerebral infarction	
Cerebral ischaemia	
Cerebrovascular accident	
Cerebrovascular disorder	
Depressed level of consciousness	
Haemorrhagic stroke	
Ischaemic stroke	
Lethargy	
Loss of consciousness	
Somnolence	
Syncope	
Transient ischaemic attack	
Vascular encephalopathy	
Vertebrobasilar insufficiency	

Abbreviation: MedDRA=Medical Dictionary for Regulatory Activities

Note: Blank in the MedDRA 15.1 column indicates no change in preferred term.

Appendix 13 List of Neoplasm Preferred Terms

Neoplastic Adverse Event Preferred Terms	
MedDRA 7.1	***MedDRA 15.1****
Acrochordon	
Adrenal adenoma	
Adrenal mass	
Basal cell carcinoma	
Benign biliary neoplasm	
Benign colonic polyp	Colonic polyp
Benign lung neoplasm	
Benign neoplasm of skin	
Benign neoplasm of thyroid gland	
Benign ovarian tumour	
Benign pancreatic neoplasm	
Benign salivary gland neoplasm	
Bile duct cancer	
Breast cancer	
Breast cancer stage III	
Breast mass	
Cervix carcinoma	
Colon cancer	
Colonic polyp	
Fibroadenoma of breast	
Gastric polyps	
Gastrointestinal cancer metastatic	
Haemangioma of liver	
Intestinal polyp	
Lipoma	
Lung neoplasm	
Metastases to liver	
Nasal polyps	
Neck mass	
Neuroendocrine tumour	
Ovarian epithelial cancer	
Pancreatic carcinoma	
Pituitary tumour benign	
Pleural neoplasm	
Prostate cancer	
Prostate cancer metastatic	
Pulmonary mass	

Neoplastic Adverse Event Preferred Terms	
MedDRA 7.1	***MedDRA 15.1****
Pyogenic granuloma	
Rectal cancer	
Rectal polyp	
Renal mass	
Skin papilloma	
Squamous cell carcinoma	
Thyroid neoplasm	
Uterine leiomyoma	
Uterine polyp	
Vocal cord polyp	

*Blank indicates no change in preferred term.

Appendix 14 Non-malignant Tumors

T1DM and T2DM Combined: List of Subjects in the Pooled, Controlled Phase 2/3 Studies with Benign Neoplasms (Safety Population of 2013 Resubmission Safety Update)

Treatment	Trial/Subject ID	Age/Sex	MedDRA Preferred Term	Investigator's Verbatim Term	Latency (days)	Discontinued
TI (TYPE 1)	MKC-TI-009/1086	41/M	Nasal polyps	Nasal polyp	373	N
	MKC-TI-009/2174	27/F	Lipoma	Lipoma	179	N
	MKC-TI-009/2278	40/M	Haemangioma of liver	Hepatic hemangioma	23	N
	MKC-TI-009/2346	29/F	Uterine polyp	Endometrial polyp	373	N
	MKC-TI-030/0295	34/F	Uterine leiomyoma	Hysteromyoma	146	N
	MKC-TI-101/899	32/M	Haemangioma of liver	Hemangioma of liver	8	N
	MKC-TI-117/0159	25/M	Thyroid neoplasm	Thyroid nodule (r)	119	N
	MKC-TI-171/1321	51/F	Colonic polyp	Benign colon polyp	99	N
	MKC-TI-171/1880	24/M	Skin papilloma	Left foot plantar wart	175	N
	MKC-TI-171/2132	59/F	Uterine leiomyoma	Myoma of uteri	118	N
TI (TYPE 2)	MKC-TI-005/8472	72/F	Pleural neoplasm	Pleural tumor 8 mm of unknown significance	115	N
	MKC-TI-030/0200	59/M	Benign neoplasm of thyroid gland	Thyroid nodule on the left lobe {benign}	672	N
	MKC-TI-030/0476	53/F	Breast mass	Palpable mass right breast	430	N
	MKC-TI-030/0918	58/M	Pituitary tumour benign	Pituitary macroadenoma	138	Y

Treatment	Trial/Subject ID	Age/Sex	MedDRA Preferred Term	Investigator's Verbatim Term	Latency (days)	Discontinued
	MKC-TI-030/0996	68/M	Nasal polyps	Nasal polyp (l)	66	N
	MKC-TI-030/1103	61/M	Colonic polyp	Colon polyp	12	N
	MKC-TI-030/1734	61/F	Skin papilloma	Papillonis at the abdomen skin	-47	N
	MKC-TI-030/1962	54/M	Colonic polyp	Colon polyps	333	N
	MKC-TI-030/1974	54/F	Uterine leiomyoma	Myomatosis of uterine	181	N
	MKC-TI-030/2098	54/M	Colonic polyp	Colon polyp (genign)	351	N
	MKC-TI-030/2440	47/F	Benign neoplasm of thyroid gland	Node of the left part of thyroid size 0.3 x 0.25 sm with microcalcinosis (size 0.1 sm){benign}	338	N
	MKC-TI-030/2902	67/M	Benign neoplasm of skin	Lump left elbow (benign skin lump)	651	N
	MKC-TI-030/2950	50/M	Lipoma	Small lipoma left abdomen	508	N
	MKC-TI-030/2973	55/M	Benign lung neoplasm	4 mm nodule lateral left lower lobe (benign)	115	N
	MKC-TI-030/3104	59/M	Vocal cord polyp	Polyp of vocal chord	378	N
			Vocal cord polyp	Polyp of vocal chord-hospitalisation	384	N
	MKC-TI-030/3367	64/M	Benign salivary gland neoplasm	Parotid gland tumor suspect (benign)	226	N
	MKC-TI-030/3399	55/M	Lipoma	Lympoma removed right lower forearm	627	N
	MKC-TI-102/1423	59/F	Lipoma	Lipoma	126	N
	MKC-TI-102/2437	54/F	Thyroid neoplasm	Thyroid node	99	N
	MKC-TI-102/5027	47/F	Uterine polyp	Endometrial polyp	382	N
	MKC-TI-103/1198	43/F	Uterine leiomyoma	Uterine fibroids (multiple)	73	N

Treatment	Trial/Subject ID	Age/Sex	MedDRA Preferred Term	Investigator's Verbatim Term	Latency (days)	Discontinued
	MKC-TI-175/3098	45/F	Lipoma	Lump to right calf lipoma	65	N
Comparator (TYPE 1)	MKC-TI-009/1151	49/F	Uterine leiomyoma	Fibroids resulting in hospitalization + hysterectomy	351	N
	MKC-TI-009/1390	36/F	Uterine leiomyoma	Fibroids	96	N
	MKC-TI-030/0597	59/M	Benign biliary neoplasm	Polyps of gall bladder {benign}	222	N
	MKC-TI-030/0736	20/F	Benign neoplasm of thyroid gland	Mid line thyroid nodule {benign}	665	N
	MKC-TI-030/3613	54/F	Uterine leiomyoma	Metrofibroma	365	N
Comparator (TYPE 2)	MKC-TI-014/353	63/F	Fibroadenoma of breast	Multiple fibroadenomatosis of mammary glands.	59	N
	MKC-TI-014/698	58/F	Gastric polyps	Gastric polyp	113	N
	MKC-TI-030/0484	63/M	Benign neoplasm of skin	Benign skin growth	160	N
	MKC-TI-030/0653	61/F	Colonic polyp	Colon polyps	329	N
	MKC-TI-030/1475	56/M	Lipoma	Fibroelastic mass on left leg (lipoma)	492	N
	MKC-TI-030/1882	63/M	Colonic polyp	Benign sessile colonic polyps	211	N
	MKC-TI-030/2104	59/M	Lipoma	Lipoma to neck and left clavicle	339	N
	MKC-TI-030/2246	57/M	Benign neoplasm of thyroid gland	Left thyroid nodule {benign}	517	N
	MKC-TI-030/2271	60/F	Thyroid neoplasm	(coloid insertion) formation d=6, 1 mm in left part of thyroid {confirmed}	675	N
	MKC-TI-030/2487	45/F	Benign neoplasm of thyroid gland	Multiple nodules in thyroid {benign}	630	N

Treatment	Trial/Subject ID	Age/Sex	MedDRA Preferred Term	Investigator's Verbatim Term	Latency (days)	Discontinued
	MKC-TI-030/3307	61/M	Lipoma	Excision lipoma right leg	33	N
	MKC-TI-030/3620	57/F	Uterine leiomyoma	Fibroma uteri	329	N
	MKC-TI-102/1338	65/F	Benign pancreatic neoplasm	Cystadenoma of pancreas	29	N
			Adrenal adenoma	Left adrenal mass benign (cortical adenoma)	29	N
	MKC-TI-102/1598	46/F	Breast mass	Right breast lump	350	N
	MKC-TI-102/2093	59/M	Rectal polyp	Bleeding palyps (rectum)	-2375	N
	MKC-TI-102/2619	42/M	Intestinal polyp	Intestinal polip	77	N
	MKC-TI-102/2701	51/F	Uterine leiomyoma	Multiple myoma (multiple hysteromyoma)	218	N
	MKC-TI-102/5023	57/M	Rectal polyp	Rectal polyps	-2	N
TP (TYPE 2)	MKC-TI-175/3644	77/F	Fibroadenoma of breast	Diffuse fibrosing adenosis of breast with areas of local fibrosis	128	N

T1DM and T2DM Combined: List of Subjects in the Pooled, Controlled Phase 2/3 Studies with Unclassified Neoplasms (Safety Population of 2013 Resubmission Safety Update)

Treatment	Trial/Subject ID	Age/Sex	MedDRA Preferred Term	Investigator's Verbatim Term	Latency (days)	Discontinued
TI (TYPE 1)	MKC-TI-009/1471	46/F	Breast mass	Breast lump	410	N
	MKC-TI-009/1478	63/M	Renal mass	Hyperdense left renal mass	358	N
	MKC-TI-009/1751	22/M	Pulmonary mass	Enlarging lung mass {per chest xrays at beginning & end of study}	378	N
	MKC-TI-009/2218	42/F	Skin papilloma	Plantar wart	176	N
	MKC-TI-030/0814	46/M	Pyogenic granuloma	Right palm pyogenic granulomg	32	N
TI (TYPE 2)	MKC-TI-030/0108	54/F	Lung neoplasm	2 cm nodular infiltrate inferior rt lobe (lungs, nodules -never biopsied)	678	N
	MKC-TI-102/1906	55/F	Lung neoplasm	Nodules in the right lung(etiology unknown)	364	N
	MKC-TI-102/3056	45/F	Skin papilloma	Verruca (2nd right finger)	60	N
	MKC-TI-102/3097	56/M	Acrochordon	Skin togs.	181	N
	MKC-TI-102/5027	47/F	Breast mass	Left breast nodule	382	N
	PDC-INS-0008/157	57/M	Lung neoplasm	4mm nodule posterior right base of lung	93	N
	PDC-INS-0008/323	54/M	Lung neoplasm	3mm nodular density right middle lobe	88	N
	PDC-INS-0008/399	37/M	Lung neoplasm	Nodular density in the right lower lobe at the cardiophrenci recess	82	N
Comparator (TYPE 1)	MKC-TI-009/1200	43/M	Lung neoplasm	Abnormal chest x-ray [indeterminate 4mm noncalcified nodule in the right middle lobe}	376	N
	MKC-TI-009/2152	47/M	Neck mass	Fatty growth tissue removal on neck	302	N

Treatment	Trial/Subject ID	Age/Sex	MedDRA Preferred Term	Investigator's Verbatim Term	Latency (days)	Discontinued
	MKC-TI-030/1583	47/M	Skin papilloma	Only surgical extirpation of veruca	85	N
Comparator (TYPE 2)	MKC-TI-030/0885	61/M	Thyroid neoplasm	Right thyroid nodule {unkinown, pt refused biopsy}	161	N
	MKC-TI-030/1764	58/M	Lung neoplasm	Lung nodule left upper lobe laterally {ncs, not identified as benign or metastic}	708	N
	MKC-TI-030/2487	45/F	Neck mass	Tumor - posterior neck {benign nodule}	591	N
	MKC-TI-030/3543	70/M	Lung neoplasm	4.5mm soft tissue nodule on (r) mid lobe {(r) middle lobe of lung}	336	N
	MKC-TI-102/2221	73/F	Lung neoplasm	Multiples micronodules on lung	365	N
	MKC-TI-102/2487	67/M	Adrenal mass	Adrenal nodule	86	N
	MKC-TI-102/5047	58/F	Skin papilloma	Verrucosis in left hand	279	N
TP (TYPE 2)	PDC-INS-0008/154	49/M	Lung neoplasm	2 mm subpleural nodular density left upper lobe	92	N
			Lung neoplasm	5mm nodular density in right upper lobe	92	N
	PDC-INS-0008/215	49/M	Adrenal mass	1.2 cm left adrenal nodule	104	N
	PDC-INS-0008/403	62/M	Lung neoplasm	3mm pulmonary nodule posterior aspect right lower lobe	88	N

List of Subjects with Focal Pulmonary Lesions/Nodules/Findings (Non-classified Lung Neoplasm)

Study/Subject ID	Age/Sex/Country/ Smoking Status/ Diabetes Type/ Treatment Duration	AE Preferred term (Verbatim term)	Radiological Findings	AE lead to withdrawal	Comment
TI					
MKC-TI-005/8472	72Year/F/ Netherlands/ Non-smoker Type 2 DM	Pleural neoplasm	On HRCT - 5mm nodule at RLL at baseline (7/9/2004); Appeared stable at follow up HRCT in Jan 2005. Nodule was not seen at the subsequent HRCT visit on April 2005.Chest x-ray in 2007 was normal.	No	Small pleural nodule seen at Baseline HRCT, disappeared 9 months later
MKC-TI-030/0108	54 year/F/USA/ Non-smoker/ T2DM/ 678 days	Lung neoplasm (2 cm nodule right side)	Baseline HRCT (Feb 2006) showed RUL, 1cm sub pleural bullae. HRCT (Jan 2008) showed a 15mm right anterior cyst. June 2008 follow up CT showed simple cyst in the same location.	Yes	Right upper lobe bullae seen at Baseline HRCT, at f/u CT 2 years later turned out to be a simple cyst
MKC-TI-102/1906	55yo/F/Poland/ Ex-smoker (19 pack years)/T2DM/ 363 days	Lung neoplasm (Nodule in the right Lung)	Chest x-ray at baseline Feb 2007 was abnormal but not clinically significant. Feb 2008, end of trial chest x-ray, showed nodule in right lung. Chest X-rays in March 2013 and Sept 2013, were normal.	No	Nodule resolved at f/u imaging studies 5 years later
PDC-INS-0008/157 Then entered into MKC-TI-010 extension study	57yo/M/ USA/ Non-smoker/ T2DM/ 92 days	Lung neoplasm (4 mm nodule right lower lobe)	Baseline CT in Feb 2004 normal; June 2004, end of study visit HRCT showed a 4mm, nodular opacity in RLL. In a subsequent HRCT nodularity resolved and may have represented atelectasis.	No	Resolved, likely atelectasis
PDC-INS-0008/323 then entered into MKC-TI-010 extension study	54yo/M/USA Non-smoker/T2DM/ 87 days	Lung neoplasm (3mm nodule RML)	Baseline HRCT May 2004 showed nodular density. June 2004, HRCT normal; Aug 2004, abnormal HRCT 3mm nodular density in the RML, July 2005, and July 2006 HRCT no change in size of nodule and no new nodules	ET due to chronic sore throat	Based on the review of serial HRCTs from over a 2 year follow-up period, lesions remained stable
PDC-INS-0008/399; then entered into MKC-TI-010 extension study	37yo/M/ USA/ Ex-smoker (2.7 pack years)/T2DM/ 81days	Lung neoplasm (nodular density right lower lobe)	July 2004, Baseline HRCT showed 10mm square-shaped opacity, pleural based, in the Superior LLL. Sept 2006, HRCT 4 mm pleural based nodule in the posterior RUL; July 2007, HRCT showed calcified lymph node in the left pulmonary hilum, nodules in both lungs, no parenchymal disease. April 2008, HRCT showed nodules unchanged and calcified lymph nodes in the left hilum,	No	Stable nodule over a 4 year f/u period with calcified hilar lymph node

Study/Subject ID	Age/Sex/Country/ Smoking Status/ Diabetes Type/ Treatment Duration	AE Preferred term (Verbatim term)	Radiological Findings	AE lead to withdrawal	Comment
MKC-TI-030/2973	55yo/M/ USA/ Non-smoker/ T2DM/114 days	Lung neoplasm (4 mm nodule LLL)	Aug 2006, Baseline HRCT Abnormal, Jan 2007, HRCT 4 mm nodule. Feb 2007, Follow-up HRCT showed complete resolution of the LLL nodule suggesting resolving focal atelectatic changes	Subject withdrew due to cough, inconvenience with product)	Likely a focal atelectasis.
PDC-INS-0008/261, then entered into MKC-TI-010 extension study	53yo/M/USA/ Smoker (17 pack years)/ T2DM/424 days	Lung neoplasm (5 mm RUL lung nodule)	Jul 2005, HRCT showed small enlarged lymph node in the anterior mediastinum. Jun 2006, HRCT 5 mm RUL nodule, Oct 2005, HRCT showed 13 mm lymph node in aortopulmonary window -unchanged from previous scan, and 8 mm lymph node (probably not seen previously because of greater between -slice interval) and no change in the 5 mm nodule; there may be 2 other tiny nodules, measuring 3 mm, one in each lobe more inferiorly. Jun 2006, HRCT normal and punctuate nodular densities in the right lung were no longer apparent. Jun 2007, HRCT showed tiny nodular opacity in the LUL anteriorly measuring 3 mm. was considered to represent a portion of a vessel	No	Anterior mediastinal lymphadenopathy and tiny nodule resolved
PDC-INS0008/ 406, then entered into MKC-TI-010 extension study	57yo/F/USA/Non-smoker T2DM/1319 days	Lung neoplasm (6.7 mm nodule in LLL)	HRCT 4/9/2010 – 9mm smooth-walled benign-appearing nodule posterior basal segment LLL. No change in size or appearance since the previous 8/19/2009 HRCT	NO	Stable nodule over one year
MKC-TI-009/1751	22yo/M/USA/Non-smoker/T1DM/ 377 days	Pulmonary mass (enlarging lung mass on chest x-ray)	Baseline x-ray Feb 2007 showed 9x 6 mm nodule on the LUL. March 2008, end of the study x-ray, showed pulmonary nodule enlarged to 13x 11 x14 mm, in addition there was a new smaller satellite 5 mm nodule in the same segment. PET scan April 2008 found lesion to be not hypermetabolic, June 2008 chest CT showed stable 10 mm nodule in LUL. Immediately medial to this nodule was a possible small 2mm daughter nodule seen on thin section imaging. April 2010, x-ray showed no change seen in the pulmonary nodule. PI reported that the subject could have had Valley fever	No	PET scan showed non hypermeatbolic lesion. Likely to be infectious etiology or inflammatory process; no further progression of the LUL lesion over 2 years and was considered to have Valley fever.

Study/Subject ID	Age/Sex/Country/ Smoking Status/ Diabetes Type/ Treatment Duration	AE Preferred term (Verbatim term)	Radiological Findings	AE lead to withdrawal	Comment
TP					
PDC-INS-0008/154 then entered into MKC-TI-010 extension study	49yo/M/USA/Non-smoker/T2DM/92 days	Lung neoplasm (2mm nodule)	March 2004, Baseline HRCT, non-significant; June 2004, HRCT showed a 2 mm sub pleural nodular density in the LUL and a 5mm nodular density in the RUL. June 2004, a follow up CT scan showed multiple calcified nodules, consistent with an old granulomatous disease.	No	Calcified nodules, consistent with granulomatous disease
PDC-INS-0008/403 then entered into MKC-TI-010 extension study	62yo/M/ USA/Non-smoker/ T2DM/ 87 days	Lung neoplasm (3 mm nodule right lower lobe))	July 2004 Baseline HRCT showed 3 x 2 cm indeterminate right para-tracheal lymph node. Oct 2004, HRCT the node remained unchanged. The HRCT also showed a 3mm pulmonary nodule in the posterior aspect of the RLL. Dec 2004 HRCT showed dense calcification of the nodular density in the RLL suggestive of a benign granuloma.	No	Calcified granuloma on the f/u HRCT
Comparator					
MKC-TI-030/1764	58yo/M/USA/Ex-smoker (52 pack years)/ 707 days	Lung neoplasm (lung nodule left upper lobe)	July 2006 Baseline chest x-ray normal; June 2007 chest x-ray, normal; June 2008, lung nodule in the LUL laterally observed. As per PI no respiratory issues since completion of the trial.	No	No f/u since left the trial.
MKC-TI-102/2221	73yo/F/ Brazil/Non-smoker/T2DM/ 357 days	Lung neoplasm (Multiple micronodules on lung)	March 2007 baseline chest x-ray normal. April 2008, end of trial chest x-ray showed multiple micro-nodules in the lung. Follow up imaging studies reveal no progression.	No	No progression of the nodules
MKC-TI-030/3543	70yo/M/ USA/Non-smoker/T2DM/ 335 days	Lung neoplasm (4.5 mm soft tissue nodule on middle lobe right lung)	Sept 2006, Baseline HRCT normal. Sept 2007, HRCT showed small 4.5 mm RML sub pleural pulmonary nodule. Aug 2008, HRCT showed no change in the RML nodule. Jan 2010, X-ray did not show presence of a pulmonary nodule.	No	Not enlarging 4.5 mm subpleural nodule resolved in HRCT 2 years later
MKC-TI-009/1200	43yo/M/USA/Ex-smoker/T1DM/ 376 days	Lung neoplasm (4 mm nodule right middle lobe)	Aug 2006, chest x-ray at baseline normal. Oct 2007, post treatment x-ray showed a 10mm ovoid nodule in the left lung base. HX. Occupational exposure to paints for 10yrs. April2008, chest x-ray, the nodule was considered to be benign.	No	Lesion was considered benign by the investigator

Appendix 15 List of Diabetic Ketoacidosis Events in T1DM and T2DM

Study/Subjec ID #	Gender/ Age/Race/ Country	Event/ Serious (Y/N)	Event Start/Stop date	Duration on Study drug	Causality	Outcome	Discontinued due to AE	Comment
Type 1 Diabetes Mellitus								
TI								
MKC-TI-030/2708	Female/42 Caucasian/ Poland	Y	02 Feb 2008 – 10 Feb 2008	372 days	Unrelated	Resolved	No	DKA was assessed secondary due to viral URI and or hepatitis due to accidental paracetamol overdose
MKC-TI-030/2805	Female/31 Caucasian/ Ukraine	Y	15 May 2007 – 5 Jun 2007	254 days	Not related	Resolved	No	Patient also was diagnosed to have acute cholecystitis with her DKA.
MKC-TI-030/2970	Female/29 Caucasian/ USA	Y	01 Nov 2006 – 03 Nov 2006	56 days	Not related	Resolved	No	Disease under study
MKC-TI-030/3493	Female/19 Caucasian/ Canada	Y	03- Nov 2006- 09 Nov 2006	33 days	Not related	Resolved	Yes	Illness of influenza and apparent lack of compliance
MKC-TI-030/3031	Female/24 Caucasian/ Czech Republic	N	13 Nov 2007- 19 Nov 2007 25 Feb-27 Feb 2008	282 days	Unrelated	Resolved	No	Ist DKA episode attributed to acute gastritis, second DKA episode attributed to acute pancreatitis.
MKC-TI-009/1546	Male /42 African American/ USA	Y	12 Jul 2007 – 15 Jul 2007	205 days	Not related	Resolved	N0	Intercurrent illness of nausea, vomiting and dehydration after eating fish was assessed as the cause of DKA. Meningitis was ruled out by CSF examination.
MKC-TI-009/1683	Male/22 Caucasian/ Poland	Y	07 Nov 2007 – 11 Nov 2007	260 days	Not related	Resolved	No	Due to dietary mistake.
MKC-TI-009/2303	Female/26 Caucasian/ Brazil	Y	05 May 2008 – 09 May 2008	362 days	Not related	Resolved	No	Missing insulin doses reported as cause of DKA.
MKC-TI-009/1522	Female/19 African American/ USA	Y	22 Dec 2006 – 29 Dec 2006	3 days	Not related	Resolved	No	Urinary tract infection, gluteal abscess and pre-existing poorly controlled diabetes was attributed as a cause of DKC
MKC-TI-009/1283	Female/33 African American/ USA	Y	11 Mar 2007 - 13 Mar 2007	146 days	Not related	Resolved	Yes	No known precipitating cause identified by the Investigator and patient was discontinued form the study.

Study/Subjec ID #	Gender/ Age/Race/ Country	Event/ Serious (Y/N)	Event Start/Stop date	Duration on Study drug	Causality	Outcome	Discontinued due to AE	Comment
MKC-TI-009/1931	Male/35 Caucasian/ USA	Y	23 Mar 2008 – 25 Mar 2008	346 days	Not related	Resolved	No	Flu-like illness and stopping both basal and prandial insulin for 3 days
MKC-TI-009/1748	Female/23 Caucasian Poland	Y	28 Feb 2007 – 02 Mar 2008	1 day	Not related	Resolved	No	No metabolic acidosis and patient was asymptomatic but her BG was 380 mg/dL, Investigator assess the cause probabaly due to improper use of the inhaler
MKC-TI-009/2242	Male/23 Caucasian Brazil	Y	23 Jan 2008 – 24 Jan 2008	265 days	Not related	Resolved	No	Intercurrent illness of acute gastroenetritis assessed as cause of DKA.
Comparator								
MKC-TI-030/0890	Female/50 Caucasian USA	Y	15 Nov 2006 - 21 Nov 2006	152 days	Not related	Resolved	No	Missed insulin assessed as cause of DKA
MKC-TI-030/1162	Female/26 Caucasian USA	Y	24 Jul 2007 – 25 Jul 2007	419 days	Not related	Resolved	No	Disease under study and intercurrent viral gastroenteritis reported as causes of DKA.
MKC-TI-030/2801	Female/30 Caucasian USA	Y	04 Feb 2008- 06 Feb 2008	515 days	Not related	Resolved	No	Causality assessed as disease under study had upper respiratory tract infection at the time of DKA.
Type 2 Diabetes Mellitus								
TI								
MKC-TI-030/2979	Female/58 Caucasian Canada	Y	11 Feb 2008 – 28 Mar 2008	339 days	Not related	Resolved	Yes	Diabetes drug regiment included sc detemir 22IU in AM and 42 IU at bedtime+ 500 mg of metformin bid; Upper respiratory tract infection, Worsening of depression led to neglect of anti-diabetic care that led to severe DKA.
Comparator								
MKC-TI-030/1952	Male/47 Caucasian Poland	Y	24 May 2008 – 28 May 2008	660 days	Not related	Resolved	No	Diabetic regimen included prandial lispro+ Humalog Mix75/25 10IU in am and 50IU in PM + Metformin 850 mg TID; Food poisoning /Intercurrent illness as cause of DKA.
MKC-TI-030/2487	Female/45 Caucasian USA	Y	17 March 2007- 23 March 2007	206 days	Not related	Resolved	No	Patient also had MI, Right bindle branch block and UTI with DKA

Appendix 16 List of Potentially Immunogenic Preferred Terms

Potentially Immunogenic Adverse Event Preferred Terms	
MedDRA 7.1	***MedDRA 15.1****
Allergic oedema	
Anaphylactic reaction	
Anaphylactic shock	
Anaphylactoid reaction	
Anaphylactoid shock	
Angioedema	
Bronchospasm	
Circumoral oedema	
Drug hypersensitivity	
Eye oedema	
Eye swelling	
Eyelid oedema	
Face oedema	
Flushing	
Generalised erythema	
Kounis syndrome	
Laryngeal dyspnoea	
Laryngeal oedema	
Laryngospasm	
Laryngotracheal oedema	
Lip oedema	
Lip swelling	
Oedema mouth	
Oropharyngeal swelling	
Periorbital oedema	
Pruritus allergic	
Pruritus generalised	
Rash erythematous	
Rash generalised	
Rash pruritic	
Skin swelling	
Stridor	
Swelling face	
Swollen tongue	
Throat tightness	
Tongue oedema	
Tracheal oedema	

Potentially Immunogenic Adverse Event Preferred Terms	
MedDRA 7.1	***MedDRA 15.1****
Type I hypersensitivity	
Urticaria	
Urticaria papular	
Wheezing	
Injection site reaction	
Application site reaction	
Administration site reaction	
Partial lypodystrophy	Partial lipodystrophy
Lypodystrophy acquired	Lipodystrophy acquired
Lypoatrophy	Lipoatrophy
Rash maculopapular	Rash maculo-papular
Dermatitis bullous	
Rash vescicular	Rash vesicular
Myalgia	
Serum sickness	

Abbreviation: MedDRA=Medical Dictionary for Regulatory Activities

Note: Blank in the MedDRA 15.1 column indicates no change in preferred term.